

8.13.2.6 SLI 381.201: A Randomized, Double-Blind, Placebo- and Active-Controlled, Crossover Study of SLI 381 in Children with Attention Deficit Hyperactivity Disorder

Final Clinical Study Report

1. TITLE PAGE

Protocol No.: 381.201

Mixed Salts Amphetamine

**A RANDOMIZED, DOUBLE-BLIND, PLACEBO- AND ACTIVE-CONTROLLED,
CROSSOVER STUDY OF SLI381 IN CHILDREN WITH
ATTENTION DEFICIT HYPERACTIVITY DISORDER**

July 31, 2000

<u>Investigator</u>	<u>Site No.</u>	<u>Location</u>
Joseph Biederman, MD	01	Boston, MA
Laurence Greenhill, MD	02	New York, NY
James McCracken, MD	03	Los Angeles, CA
James Swanson, PhD	04 (lead investigator)	Irvine, CA

Study Start Date: September 21, 1999

Study Stop Date: December 4, 1999

Sponsor: Shire Laboratories, Inc
1550 East Gude Drive
Rockville, MD 20850

Contact Person: Yuxin Zhang, PhD

10-5948

This study was conducted in compliance with internal review board and informed consent regulations.

Name of Study Drug: Mixed Salts Amphetamine	IND #: [REDACTED]	Protocol No. 381.201	Phase: II	Country: USA
Number of Subjects (planned and analyzed): The protocol called for 60 subjects to be randomized in order that 36 subjects complete the study, to provide 90 percent power to detect a statistical difference in SKAMP ratings at an alpha level of 0.05 (2-tailed). An effect size of 1.0 was assumed. Fifty-one subjects enrolled in to the study and all of them were randomized with 44 subjects completing the study.				
Diagnosis and Main Criteria for Inclusion: Subjects were aged 6 to 12 years, had satisfied DSM-IV criteria diagnosis of ADHD, combined or hyperactive subtypes, and were on a stable regimen and daily dose of Adderall® dextroamphetamine, or methylphenidate without unacceptable side effects. Eligible patients were washed out for 7 days prior to entering the practice visit (Visit 2).				
Test Product, Dose, Mode of Administration, and Batch Number: Study medications included SLI381 10 mg (Batch No. 9F2797), SLI381 20 mg (Batch No. 9F2702), and SLI381 30 mg (Batch No. 9F2703) capsules given orally once each day in the morning.				
Duration of Treatment: Prior to being randomized into the double-blind treatment, all subjects were dosed with a single SLI381 20 mg dose at Visit 2 (practice visit). During the double-blind phase, subjects received daily study medication for one week with each of 5 treatments (including placebo) plus one make-up week, resulting in a total of 6 double-blind treatment weeks.				
Reference Therapy, Dose and Mode of Administration, Batch Number: The sponsor provided Adderall® 10 mg in capsules (Batch No. B8461) and matching placebo capsules (Batch No. GUS00515.06) given orally once each day in the morning.				
Criteria for Evaluation: Efficacy: The Swanson, Kotkin, Agler, M-Flynn, and Pelham (SKAMP) Rating Scale and the Permanent Product Measure of Performance (PERMP) Derived Measures constituted the primary efficacy variables. The SKAMP is a rating scale with 8 core items and used by independent observers to rate the behavior of children during an analog classroom session(s). Each item is rated on a 7-point impairment scale (0 = normal, 6 = maximal impairment). Items are specific to place (classroom setting) and time (during a typical classroom period), and the scale is used to collect multiple ratings during a laboratory school day. The SKAMP was completed at Visits 2, 3, 4, 5, 6, 7, and 8. The PERMP is a 10-minute written math test taken in the classroom. The test consists of 4 pages of math problems, appropriate to a child's age. Subjects are instructed to work at their desks and to complete as many problems as possible in 10 minutes. Efficacy is measured using the number of problems worked correctly and number of problems attempted by the subject. The PERMP was administered at Visits 2, 3, 4, 5, 6, 7, and 8. During each laboratory school day, the SKAMP and PERMP were completed during classroom cycles at approximately 0.5, 1.5, 4.5, 6.0, 7.5, 9.0, 10.5, and 12 hours post dose. For the primary efficacy analyses, the SKAMP and PERMP were analyzed for the Intent-to-Treat (ITT) population. For the secondary efficacy analyses, both measures were analyzed for the Per Protocol (PP) population.				

Name of Study Drug: Mixed Salts Amphetamine	IND #: [REDACTED]	Protocol No. 381.201	Phase: II	Country: USA
<p>Criteria for Evaluation: (cont'd)</p> <p>Pharmacokinetic: Blood samples were collected to assess plasma levels of d- and l-amphetamine for all subjects immediately before dosing, at 0.5, 1.5, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, and 12.0-hours post dose, as well as 24 hours post dose, both during the practice visit (Visit 2) for a single 20 mg dose of SLI381 and the last visit (Visit 8) following the 7th day dosing with each of the five treatments. Plasma concentrations and PK parameters were calculated for each subject. Plasma levels of both d-amphetamine and l-amphetamine were related to efficacy measures, using Pearson correlation coefficient, to assess PK/PD relationship.</p> <p>Safety: All safety parameters collected were assessed descriptively. These parameters included adverse medical experiences (AMEs), clinical laboratory tests (chemistry, hematology, and urinalysis), medical history, physical examination, and vital signs. In addition, side effect ratings collected from parents once each week and from teachers at the end of each laboratory school day were assessed.</p>				
<p>Statistical Methods:</p> <p>Efficacy: The primary efficacy analysis was conducted on the ITT population, using a mixed-effect model of analysis of variance (ANOVA). The model had subject nested within site as random effect, and treatment, period, session, and the treatment-by-session interaction as fixed effects. Given a significant treatment and/or treatment-by-session effect ($p < 0.05$), pairwise comparisons among individual treatments were further conducted for each session. Specifically, planned pairwise contrasts were done, using linear contrasts, to compare each of the SLI381 treatments with placebo and with Adderall[®] within each session. This analysis was repeated for both SKAMP and PERMP measures. The secondary efficacy analysis consisted of performing the same analyses for the SKAMP and PERMP measures for the PP population.</p> <p>Pharmacokinetic: Descriptive statistics of pharmacokinetic parameters following a single SLI381 20 mg dose were reported for both d- and l-isomers. These parameters included C_{max}, AUC_{0-24}, and T_{max}. Average plasma drug concentration plot over time was reported.</p> <p>Descriptive statistics of pharmacokinetic parameters following multiple doses, obtained during the last day of the make-up week (Visit 8) were reported for each treatment. These parameters included C_{max}, AUC_{0-24}, and T_{max}. Average plasma drug concentration plots over time were presented for each of the 5 treatments. The steady-state PK parameters were also analyzed comparatively for treatment differences using one-way ANOVA with treatment as the factor. In addition, plasma drug concentrations for the SLI381 10 mg vs. Adderall[®] 10 mg were analyzed at each sampling time point, using a 2-group t-test (2-sided). Statistical significance was tested at the 5% level.</p> <p>PK/PD relationship: The pharmacokinetic/pharmacodynamic (PK/PD) relationship was analyzed visually by plotting the corresponding PD data obtained during Visit 8 in the same graph with the plasma concentration data for each treatment. Correlation was assessed using Pearson correlation coefficients between the plasma levels and SKAMP/PERMP scores for each patient. The mean correlation with 95% confidence interval was reported for each treatment. The analysis was carried out for both d-amphetamine and l-amphetamine.</p> <p>Safety: Observed adverse medical experiences (AMEs), coded with COSTART V terminology, were analyzed comparatively using paired t-test for each of the SLI381 treatment vs. either Adderall[®] or placebo. AMEs were counted only once for each body system and preferred term for all incidence tables.</p>				

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:		
Mixed Salts Amphetamine		381.201	II	USA		
Statistical Methods: (continued)						
Safety: (continued)						
Descriptive statistics of vital signs were reported for each treatment at pre- and post dose. Changes in clinical laboratory tests from pre-treatment (Visit 2) to end of study (Visit 8) were reported for all the subjects. Clinically significant changes in clinical laboratory tests were tabulated. Descriptive statistics of side effect ratings collected from both parents and teachers were reported for each treatment.						
SUMMARY RESULTS:						
EFFICACY:						
The mixed-effect ANOVA disclosed highly significant overall treatment effect (averaged across the scores of the 8 sessions observed under the treatment) for all of the efficacy measures ($p < 0.0001$). Pairwise comparisons of active doses vs. placebo on the overall treatment average indicated that for all of the four measures, significant improvements were seen in favor of the SLI381 doses ($p < 0.0001$) and Adderall 10 mg ($p < 0.001$). Results of the time course evaluation are tabulated below for each efficacy measure:						
Measure	Time (hr) post dose	Average Score				
		Placebo	Adderall 10 mg	SLI381 10 mg	SLI381 20 mg	SLI381 30 mg
SKAMP Attention	0.0	1.18	1.59**	1.55*	1.27	1.38
	1.5	1.31	0.88**	1.27	1.16	0.98**
	4.5	1.40	0.92***	1.13*	1.07**	0.90***
	6.0	1.74	1.26***	1.26***	1.14***	0.74***
	7.5	1.73	1.22***	1.21***	1.13***	0.74***
	9.0	1.51	1.55	1.40	1.26**	1.05***
	10.5	1.74	1.60	1.40**	1.27***	1.23***
	12.0	1.44	1.59	1.23	1.18**	1.15**
SKAMP Deportment	0.0	1.88	2.43**	2.28	2.26	1.96
	1.5	2.22	1.08***	1.91	1.69**	1.58***
	4.5	2.28	1.25***	1.80**	1.22***	0.90***
	6.0	2.88	1.70***	1.85***	1.84***	1.13***
	7.5	2.90	1.94***	2.13***	1.67***	1.29***
	9.0	2.82	2.04***	2.35**	1.79***	1.46***
	10.5	2.66	2.17*	2.44	2.15**	1.45***
	12.0	1.99	1.91	2.15	1.73	1.59**
PERMP number attempted	0.0	89.43	59.37***	63.71**	68.36*	80.39
	1.5	88.61	118.86***	102.62	102.87*	110.98**
	4.5	85.61	100.21	106.12*	111.48***	131.29***
	6.0	69.16	95.83**	102.62***	120.87***	127.90***
	7.5	60.39	81.16*	87.85**	107.87***	120.12***
	9.0	60.18	84.40**	79.80*	89.27***	108.19***
	10.5	58.05	62.21	78.95*	90.07***	100.20***
	12.0	73.48	73.37	72.43	91.77**	95.63**
PERMP number correct	0.0	86.77	56.20***	60.95***	65.39*	77.78
	1.5	85.20	112.72***	97.74	98.11*	105.52**
	4.5	77.77	94.69*	102.12**	107.18***	123.79***
	6.0	63.23	90.29***	97.90***	112.49***	124.52***
	7.5	57.34	72.58	82.12**	103.80***	115.55***
	9.0	54.23	73.40*	74.44*	85.64***	105.02***
	10.5	50.17	60.40	73.55**	86.16***	97.39***
	12.0	64.88	67.78	68.85	87.25***	92.54***

* $p < 0.05$; ** $p < 0.01$; *** $p < 0.001$ compared with placebo using planned pair-wise contrasts, following mixed-effects ANOVA

Name of Study Drug: Mixed Salts Amphetamine	IND #: [REDACTED]	Protocol No. 381.201	Phase: II	Country: USA
SUMMARY RESULTS: (continued)				
EFFICACY: (continued)				
<p>When compared with placebo, SLI381 30 mg showed significantly lower average scores ($p < 0.01$) at all of the time points from 1.5 to 12.0 hours post dose for both SKAMP attention and deportment; SLI381 20 mg also showed significantly lower average scores ($p < 0.01$) at all of the time points from 1.5 to 12.0 hours post dose for SKAMP attention and deportment, with 2 exceptions (attention at 1.5 hours and deportment at 12.0 hours); SLI381 10 mg demonstrated significantly lower average scores ($p < 0.05$) at the time points from 4.5 to 10.5 hours post dose for SKAMP attention and deportment, with 2 exceptions (attention at 9.0 hours and deportment at 10.5 hours); and Adderall® 10 mg had significantly lower average scores ($p < 0.05$) at the time points from 1.5 to 7.5 hours post dose for SKAMP attention and from 1.5 to 10.5 hours post dose for SKAMP deportment.</p>				
<p>For PERMP, when compared with placebo, SLI381 30 mg showed significantly higher average scores ($p < 0.01$) at all of the time points from 1.5 to 12.0 hours post dose for both PERMP number attempted and number correct; SLI381 20 mg also showed significantly higher average scores ($p < 0.05$) at all of the time points from 1.5 to 12.0 hours post dose for PERMP number attempted and number correct; SLI381 10 mg demonstrated significantly higher average scores ($p < 0.05$) at the time points from 4.5 to 10.5 hours post dose for PERMP number attempted and number correct; and Adderall® 10 mg had significantly higher average scores ($p < 0.05$) at the time points from 1.5 to 9.0 hours post dose for PERMP number attempted and from 4.5 to 10.5 hours post dose for PERMP number correct, with 2 exceptions (number attempted at 4.5 hours and number correct at 7.5 hours post dose).</p>				
PHARMACOKINETICS:				
<p>Following a single dose administration of SLI381 20 mg, the T_{max} (hr) was 6.78 and 6.94 for d- and l-amphetamine, respectively; C_{max} (ng/mL) was 48.81 and 14.80; and AUC_{0-24} (ng.hr/mL) was 703.91 and 216.20.</p>				
<p>For d-amphetamine, after one week daily administration of SLI381 30 mg, 20 mg, or 10 mg, the C_{max} (ng/mL) was 89.04, 54.63, and 28.82, respectively; AUC_{0-24} (ng.hr/mL) was 1364.37, 777.24, and 431.88, respectively; and the T_{max} (hr) was 5.50, 5.83, and 6.38, respectively, compared to about 3.33 hours for Adderall® 10 mg. For l-amphetamine, after one week daily administration of SLI381 30 mg, 20 mg, or 10 mg, the C_{max} (ng/mL) was 28.08, 17.15, and 8.82, respectively; AUC_{0-24} (ng.hr/mL) was 443.53, 261.63, and 138.34, respectively; and the T_{max} (hr) was 5.50, 5.67, and 6.38, respectively, compared to 3.22 hours for Adderall® 10 mg.</p>				
PK/PD RELATIONSHIP:				
<p>The mean Pearson correlation coefficients of d- and l-amphetamine levels with the SKAMP scores were all negative, ranging from -0.067 to -0.388. The mean Pearson correlation coefficients of d- and l-amphetamine levels with the PERMP scores were all positive, ranging from 0.410 to 0.473. The findings indicated a moderate relationship between plasma drug levels and pharmacodynamic measures for amphetamine.</p>				

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine	[REDACTED]	381.201	II	USA
SAFETY:				
<p>During the double-blind period of the study, subjects reported a total of 919 AMEs post randomization, and both the overall incidences and term-specific incidences of AMEs were similar across the 5 treatment groups, including placebo. No serious AMEs or deaths were reported. No AMEs were deemed definitely treatment-related by investigators. The most commonly reported AMEs were nervousness, anorexia, abdominal pain, insomnia, and headache.</p>				
<p>Two (4%) of 51 subjects randomized were discontinued from the study due to AMEs: one subject on placebo withdrawn due to agitation and the other on SLI381 20 mg withdrawn due to stomach ache.</p>				
<p>Mean values for clinical laboratory tests, vital signs, and the side effect ratings were similar between treatments. Abnormal chemistry, hematology, and urinalysis results were sporadic and infrequent.</p>				
CONCLUSIONS:				
<p>The objective of this study was to evaluate the efficacy and safety of three SLI381 doses (10 mg, 20 mg, 30 mg), compared to placebo and Adderall® 10 mg, to assess the time course of the therapeutic response to treatment, and to examine the pharmacokinetic profile of SLI381 after a single 20 mg dose and at steady state for the three SLI381 doses under study.</p>				
<p>ITT analysis disclosed highly significant overall treatment effect (averaged across the scores of the 8 sessions observed under the treatment) for all of the efficacy measures). Pairwise comparisons of active doses vs. placebo on the overall treatment average indicated that for all of the four measures, significant improvements were seen in favor of the SLI381 doses and Adderall 10 mg. Further analyses revealed significant time course effects for all active treatment groups vs placebo and dose-dependent improvements with SLI381. Placebo-treated subjects showed a pattern of deterioration over the course of the 12-hour observation period. This time-related deterioration from initial performance was most notable for the PERMP measures. In contrast, SLI381 30 mg, 20 mg, and 10 mg as well as Adderall® 10 mg showed rapid improvement in efficacy measures by 1.5 hours post dose, both compared with placebo and initial performance (i.e., the first classroom session). In comparison to placebo, SLI381 30 mg, 20 mg, and 10 mg showed continued significant efficacy up to 10.5 to 12 hours post dose for efficacy measures; in contrast, Adderall® 10 mg revealed efficacy up to 9 hours post dose.</p>				
<p>Compared to a single 20 mg dose, the amount of drug accumulation after one week daily administration of SLI381 20 mg was very small as measured by area under the curve. After one week of daily administration, the T_{max} of SLI381 10 mg was about 6.4 hours for both d- and l-amphetamine, which was approximately twice as long as that of Adderall® 10 mg.</p>				
<p>In addition, the study observed a moderate relationship between plasma drug levels and pharmacodynamic measures for amphetamine.</p>				
<p>A total of 919 AMEs were reported post randomization in the study. Most of the AMEs were mild or moderate in intensity. None of the AMEs were considered definitely treatment-related. The incidence of subjects reporting AMEs was similar across the 5 treatments. No unusual or serious AMEs were reported. The most commonly reported AMEs were nervousness, anorexia, abdominal pain, insomnia, and headache, all of which are typical side effects of amphetamines.</p>				
<p>SLI381 appears to be an efficacious treatment for childhood ADHD. Depending upon doses, rapid onset occurred within the hour of dosing with amphetamine. The persistence of effect of SLI381 doses lasted throughout the day and into early evening, for a duration of about 10 to 12 hours, suggesting that this medication provides a longer duration of action. Maintenance of amphetamine concentrations is sufficient to extend the duration of action of the drug. There appears to be a clear dose response with SLI381 in terms of efficacy. SLI381 doses appear to be safe and well-tolerated.</p>				

3. TABLE OF CONTENTS	
1. TITLE PAGE	I
2. SYNOPSIS	II
3. TABLE OF CONTENTS	1
3.1 LIST OF IN-TEXT TABLES.....	5
3.2 LIST OF IN-TEXT FIGURES.....	6
4. GLOSSARY AND DEFINITION OF TERMS	7
5. ETHICS	8
5.1 INSTITUTIONAL REVIEW BOARD.....	8
5.2 ETHICAL CONDUCT OF THE STUDY	8
5.3 SUBJECT INFORMATION AND CONSENT.....	8
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE	9
7. INTRODUCTION.....	9
8. STUDY OBJECTIVES.....	11
9. INVESTIGATIONAL PLAN.....	11
9.1 OVERALL STUDY DESIGN AND PLAN.....	11
9.1.1 Schedule of Assessments	11
9.1.2 Screening (Visit 1) and Washout Period	12
9.1.3 Practice Visit (Visit 2).....	13
9.1.4 Double-blind Treatment (Visits 3 – 8).....	13
9.1.5 Final Study Visit (Visit 8).....	14
9.2 CLASSROOM PROCEDURES.....	14
9.2.1 Recommended Staff	14
9.2.2 Timing and Sequence of Events	15
9.2.3 Group Academic Activities	16
9.2.4 Recess Activities.....	16
9.3 CHOICE OF CONTROL GROUPS.....	17
9.4 SELECTION OF STUDY POPULATION.....	17
9.4.1 Inclusion Criteria	17
9.4.2 Exclusion Criteria.....	17
9.4.3 Diagnostic Criteria.....	18
9.4.4 Removal of Subjects from Therapy or Assessment.....	19

9.5 TREATMENTS.....	20
9.5.1 Treatments Administered.....	20
9.5.2 Identity of Study Drug.....	20
9.5.3 Method of Assigning Subjects to Treatments.....	21
9.5.4 Dose Selection.....	21
9.5.5 Blinding.....	21
9.5.6 Prior and Concomitant Illnesses and Treatments.....	22
9.5.7 Treatment Compliance.....	23
9.5.8 Drug Accountability.....	23
9.6 EFFICACY AND SAFETY VARIABLES.....	23
9.6.1 Efficacy Parameters.....	23
9.6.2 Pharmacokinetic Parameters.....	24
9.6.3 Safety Evaluations.....	24
9.6.4 Appropriateness of Measurements.....	27
9.7 DATA QUALITY ASSURANCE.....	27
9.7.1 Standardization Procedures.....	27
9.7.2 Monitoring and Auditing.....	28
9.7.3 Data Management.....	28
9.8 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE.....	29
9.8.1 Statistical and Analytical Plans.....	29
9.8.2 Determination of Sample Size.....	32
9.9 CHANGES IN THE CONDUCT OF THE STUDY OR THE PLANNED ANALYSES.....	33
9.9.1 Changes in the Conduct of the Study.....	33
9.9.2 Changes in the Statistical Analysis.....	33
10. SUBJECT GROUPS.....	37
10.1 DISPOSITION OF SUBJECTS.....	37
10.2 PROTOCOL DEVIATIONS.....	39
11. EFFICACY EVALUATION.....	39
11.1 DATA SETS ANALYZED.....	40
11.1.1 Intent-to Treat (ITT) Data Set.....	40
11.1.2 Per Protocol (PP) Data Set.....	40
11.2 DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS.....	40
11.3 MEASUREMENTS OF TREATMENT COMPLIANCE.....	41
11.4 EFFICACY RESULTS.....	42
11.4.1 Primary Efficacy Analysis.....	42

11.4.2	Secondary Efficacy Analyses	53
11.4.3	Pharmacokinetic Analysis	56
11.5	EFFICACY CONCLUSIONS	59
12.	SAFETY EVALUATION	60
12.1	DATA SETS ANALYZED	60
12.2	EXTENT OF EXPOSURE	61
12.3	ADVERSE MEDICAL EXPERIENCES (AMES)	61
12.3.1	Brief Summary of Adverse Medical Experiences	61
12.3.2	Number and Percent of Subjects Reporting Adverse Medical Experiences	61
12.4	DEATHS, OTHER SERIOUS ADVERSE EVENTS, SUBJECTS WITHDRAWN FOR AMES, AND OTHER SIGNIFICANT ADVERSE EVENTS	63
12.4.1	Deaths	63
12.4.2	Other Serious Adverse Medical Experiences	63
12.4.3	Other Significant Adverse Medical Experiences	63
12.4.4	Subjects Withdrawn for Adverse Medical Experiences	63
12.4.5	Narratives of Subjects Withdrawn for Adverse Medical Experiences	63
12.5	CLINICAL LABORATORY RESULTS	64
12.5.1	Hematology	64
12.5.2	Chemistry	64
12.5.3	Urinalysis	65
12.6	VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY	65
12.6.1	Vital Signs	65
12.6.2	Physical Examinations	65
12.6.3	Medical History	65
12.6.4	Other Safety Measures	65
12.7	SAFETY CONCLUSIONS	66
13.	DISCUSSION AND OVERALL CONCLUSIONS	66
14.	REFERENCED TABLES AND FIGURES NOT INCLUDED IN THE TEXT	69
15.	REFERENCES	200
16.	APPENDICES	201
APPENDIX IA:	1) Laboratory Test Reference Values 2) CRFs of Subjects Withdrawn Due to Adverse Events	
APPENDIX IB:	General IND Information	

- APPENDIX IIA: Protocol Cover Sheet/Protocol
- APPENDIX IIB: Blank Case Report Form
- APPENDIX IIC: IRB Information
- APPENDIX III: Publications of Results
- APPENDIX IV: Location of Studies and Investigators
- APPENDIX V: Subject Randomization
- APPENDIX VIA: Detailed Statistical Documentation
- APPENDIX VIB: Detailed Pharmaceutical Analytical Report/Technical Report
- APPENDIX VII: Subject Data Listings

3.1 List of In-Text Tables

TABLE 1	SCHEDULE OF ASSESSMENTS.....	12
TABLE 2	SCHEDULE OF ACTIVITIES ACROSS THE DAY.....	16
TABLE 3	STATISTICAL ANALYSIS CLARIFICATIONS.....	34
TABLE 4	SUBJECT DISPOSITION.....	37
TABLE 5	EARLY TERMINATIONS.....	38
TABLE 6	SUMMARY OF SUBJECT DEMOGRAPHIC AND BASELINE CHARACTERISTICS.....	42
TABLE 7	MEAN SCORES (SD) OF SKAMP RATING SCALE: ATTENTION.....	44
TABLE 8	MEAN SCORES (SD) OF SKAMP RATING SCALE: DEPORTMENT.....	46
TABLE 9	MEAN SCORES (SD) OF PERMP RATING SCALE: NUMBER ATTEMPTED.....	49
TABLE 10	MEAN SCORES (SD) OF PERMP RATING SCALE: NUMBER CORRECT.....	51
TABLE 11	AUC ₀₋₂₄ , AUC _{0-12h} , C _{MAX} AND T _{MAX} AFTER SINGLE 20 MG DOSE.....	56
TABLE 12	AUC ₀₋₂₄ , C _{MAX} AND T _{MAX} AT STEADY STATE DURING FINAL WEEK.....	57
TABLE 13	CORRELATION COEFFICIENTS (R) BETWEEN D- AND L-AMPHETAMINE LEVELS AND PHARMACODYNAMIC MEASURES DURING FINAL WEEK.....	58
TABLE 14	SUBJECT DRUG EXPOSURE DURING RANDOMIZED PHASE (N=51).....	61
TABLE 15	NUMBER (%) OF SUBJECTS REPORTING POST RANDOMIZATION ADVERSE MEDICAL EXPERIENCES (≥ 10% OF ANY TREATMENT).....	62
TABLE 16	NUMBER OF POST RANDOMIZATION ADVERSE MEDICAL EXPERIENCES REPORTED (≥ 10 EPISODES IN ANY TREATMENT).....	63

3.2 List of In-Text Figures

- FIGURE 1 MEAN SKAMP ATTENTION SCORE BY TREATMENT AND CLASSROOM SESSION (ITT).... 45
- FIGURE 2 MEAN SKAMP DEPORTMENT SCORE BY TREATMENT AND CLASSROOM SESSION (ITT). 47
- FIGURE 3 MEAN PERMP NUMBER ATTEMPTED BY TREATMENT AND CLASSROOM SESSION (ITT) 50
- FIGURE 4 MEAN PERMP NUMBER CORRECT BY TREATMENT AND CLASSROOM SESSION (ITT).... 52

4. GLOSSARY AND DEFINITION OF TERMS

ADHD	attention deficit hyperactivity disorder
AME	adverse medical experience
ANOVA	analysis of variance
ALT	alanine aminotransferase
AST	aspartate aminotransferase
AUC	area under the plasma-concentration time curve
AUC ₀₋₂₄	area under the concentration time profile (0 to last data point)
AUC _{0-inf}	area under the concentration time profile (0 to infinity)
AUC _{0-t}	area under the concentration time profile (0 to t hour)
CFR	Code of Federal Regulations
CRF	case report form
C _{min}	minimum plasma drug concentration
C _{max}	maximum plasma drug concentration
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
DISC- 4.0	Diagnostic Interview Schedule-Children- Version 4.0
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4th ed.
GCP	good clinical practice
Ingenix	Ingenix Pharmaceutical Services
IRB	institutional review board
ITT	Intent-to-Treat
NIMH	National Institute of Mental Health
PERMP	Permanent Product Measure of Performance (math tests)
PD	pharmacodynamics
PK	pharmacokinetics
PP	Per Protocol
SAE	serious adverse event
SKAMP	Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale
t _{1/2}	half life
T _{max}	time to maximum drug concentration
WBC	white blood cell (count)

5. ETHICS

5.1 Institutional Review Board

The study protocol, informed assent and consent form, and any amendments to the protocol were approved by site institutional review boards (IRBs), prior to study initiation, in conformance with 21 CFR 50 and 21 CFR 56. The approval letters are on file at Shire. Information about all IRBs is given in *Section 16, Appendix IIC, IRB Information*.

5.2 Ethical Conduct of the Study

The study was conducted in accordance with good clinical practice (GCP) and the standard operating procedures for clinical investigation and documentation in force at Shire Laboratories, Inc. (Shire) and Ingenix Pharmaceutical Services (Ingenix; formerly Worldwide Clinical Trials). Compliance with these requirements also indicates conformity with the ethical principles that have their origins in the Declaration of Helsinki. A trial master file containing essential documents for this study has been established and archived at Shire, with additional copies of essential documents on file at Ingenix.

5.3 Subject Information and Consent

Written informed assent with parental or guardian consent was obtained for each subject prior to performance of any protocol-related activities. As part of this procedure, the principal investigator or one of his or her associates explained orally and in writing the nature, duration, and purpose of the study, and the action of all study drugs in such a manner that the subject and appointed guardian were made aware of the potential risks, inconveniences, or adverse effects that might occur. They also were informed that the subject could withdraw from the study at any time. A signed statement by the child's parent or guardian was minimally required to show the child's assent to participate. (For example, "This research study has been explained to my child _____ in my presence, in language he or she can understand. He or she has been encouraged to ask questions both now and in the future, about the research study. He or she has assented to take part in this research study.") Failure on the part of the child to object was not to be considered assent. Affirmative agreement by the child was required. The subject and parent (or guardian) were to receive all information required by federal regulations. The principal investigator was to provide the sponsor with a copy of the IRB-approved informed consent form prior to the start of the study.

The sample informed assent/consent form was written in compliance with U.S. federal regulation 21 CFR Part 50 and other national regulations as appropriate and was made available to each investigative site to use in preparing site-specific versions. The sample subject assent/consent form is provided in *Section 16, Appendix IIC, IRB Information*. Site-specific versions are on file with the sponsor and are available upon request.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted at 4 sites. The list of investigators can be found in *Section 16, Appendix IV, Location of Studies and Investigators*. Prior to the initiation of the study, a practice session with all 4 investigators present was conducted at the University of California – Irvine, under the direction of the lead investigator, James Swanson, PhD. The study administrative structure is shown below.

<u>Name and Affiliation</u>	<u>Title</u>	<u>Role</u>
James Swanson, PhD University of California—Irvine	Lead Investigator	Conduct study and provide overall guidance
Joseph Biederman, MD Massachusetts General Hospital	Investigator	Conduct study
Laurence Greenhill, MD NY State Psychiatric Institute	Investigator	Conduct study
James McCracken, MD UCLA Neuropsychiatric Institute	Investigator	Conduct study
Shire Laboratories Inc Simon Tulloch, MD	SVP, US R&D	Overall responsibility for clinical and safety aspects of the study
Beth McGrain	Associate Director, Clinical Research	Sponsor's supervisory contact for study management
Kathleen O'Brien	Clinical Program Manager	Sponsor's primary contact for study management
Ingenix Pharmaceutical Services Gaston Farr	Project Manager	Study management
Doniel Jackson, MD	Medical Monitor	Oversee clinical and safety aspects of study

7. INTRODUCTION

Stimulant medications have been used successfully to treat attention deficit hyperactivity disorder (ADHD) in children for many years, and a recent National Institute of Mental Health (NIMH) consensus meeting has suggested that stimulant medications are the single best therapeutic agent in treating symptoms of ADHD in children.

Swanson et al (1998) conducted a representative clinical trial with Adderall[®], a stimulant medication, in children with ADHD. This randomized, double-blind, crossover study evaluated the safety and time-course effects of 4 doses of Adderall[®] (5, 10, 15, and 20 mg), an active control (clinical dose of methylphenidate), and a placebo control in an analog classroom setting. This study showed no unexpected or serious side effects and demonstrated differences in time-response patterns between Adderall[®] doses and methylphenidate that may help tailor treatment to meet specific clinical needs of different children with ADHD.

Despite the effectiveness of Adderall® in treating various symptoms of ADHD, several potential problems may arise when pediatric subjects are required to take stimulant medications multiple times during the day, especially when medication needs to be administered during the school day. School-time dosing creates issues related to compliance, privacy, and the potential diversion of doses. In addition, clinicians anecdotally have suggested significant variations in behavior related to the estimated peak and trough levels of stimulant medications related to dosing levels and intervals between dosing. Given these factors, there is a need for an effective formulation of a stimulant medication which, when given in the morning, produces a relatively quick therapeutic effect that lasts throughout the school day, eliminating the need for a midday dose during the school day.

Shire Laboratories Inc. has developed a 2-component extended-release formulation (SLI381 capsules) of Adderall® designed to produce pulsed-release of amphetamine salts yielding a therapeutic effect that lasts throughout the day with one morning dose for treatment of attention deficit hyperactivity disorder (ADHD) and narcolepsy.

Adderall® is a single entity amphetamine drug product mixture of neutral salts of dextroamphetamine sulfate, amphetamine sulfate, the dextro isomer of amphetamine saccharate, and d, l-amphetamine aspartate. For each Adderall® tablet, the combination of salts and isomers results in a 3:1 ratio of dextro- to laevo-amphetamine.

The SLI381 capsule formulation is composed of 2 types of pellets of mixed salts of amphetamine being combined with a 50:50 ratio within one capsule. One type of pellet is an immediate-release pellet designed to release drug content in a mechanism similar to Adderall®. The second type of pellet is a delayed-release pellet designed to release drug content 4-6 hours after the oral administration. With the inclusion of the delayed-release component, the 2-unit formulation, given once a day, is expected to act similarly to the currently marketed product of Adderall® given twice a day, 4-6 hours apart.

A pilot study (Protocol # 381.102) compared the bioavailability of three composite 20 mg experimental formulation qd against the reference, Adderall® 10 mg bid with a 4-hour interval. The selected SLI381 formulation was bioequivalent to Adderall in terms of the d- and l-amphetamine extent and rate of absorption. The time to maximum concentration values for d- and l-amphetamine were not different to those of observed for Adderall®.

The purpose of this Phase II study was to assess the safety and efficacy of various SLI381 doses (10 mg, 20 mg, and 30 mg) in an analog classroom setting, compared to placebo and Adderall® 10 mg dose, using a crossover design with repeated measures taken during each testing day. This design allowed for the evaluation of the duration of drug action of SLI381 doses during a treatment day with reference to either placebo or Adderall® 10 mg dose.

The study was conducted in compliance with institutional review board and informed consent regulations.

Final
Date: July 31, 2000

10-5963

8. STUDY OBJECTIVES

Primary: To assess, under controlled conditions, the efficacy and safety of SLI381 10, 20, and 30 mg compared with placebo and with Adderall® 10 mg administered once daily in the morning to children with ADHD by Diagnostic and Statistical Manual of Mental Disorders, 4th ed (DSM-IV) criteria.

Secondary:

- To assess the morning and afternoon therapeutic responses to SLI381.
- To examine the pharmacokinetic (PK) profile of SLI381 after single dose and at steady state.

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This was a randomized, multicenter, double-blind, placebo- and active-controlled, crossover, multiple-dose study of 3 doses of SLI381 (10 mg, 20 mg, 30 mg) vs. one Adderall® 10 mg dose vs. placebo in children diagnosed with ADHD according to DSM-IV criteria. There were 4 study centers participating in this trial. Each center was asked to randomize 15 subjects to yield a theoretical study maximum of 60 subjects randomized with approximately 36 subjects completing.

The study consisted of 3 parts: a screening period, a single-dose classroom practice day with a minimum 1-week lead-in washout, and a 6-week double-blind medication period. Subjects randomized into the double-blind treatment received 1 morning dose of one of the 5 treatments for 1 week, and crossed over to the remaining alternative treatments for the subsequent weeks, according to the pre-prepared site-specific randomization schedule of a 5x5 Latin square. The sixth double-blind week was a make-up week intended for duplication of one of the 5 treatments. A separate randomization schedule was prepared for the make-up week for each center.

The classroom day occurred on the last day of each double-blind treatment week, including the 5 core treatment weeks and the make-up week. Eight classroom sessions were arranged on each classroom day at 0.0, 1.5, 4.5, 6.0, 7.5, 9.0, 10.5, and 12.0 hours post dose (study medication was administered to the subject in the morning around 7:30 a.m. in the laboratory school). Efficacy measures were observed during each of these classroom sessions.

9.1.1 Schedule of Assessments

The procedures that were performed throughout the study are outlined in Table 1. Unless otherwise indicated, all assessments listed below were to be performed by the investigator or other regular study personnel. If the subject terminated treatment early, all

assessments called for at the final visit (Visit 8) were to be completed at the termination visit.

Table 1 Schedule of Assessments

Activity	Screening	Practice	Double-blind						
	Visit Number:	1	2	3	4	5	6	7	8 ^a
Week Number:	--	0	1	2	3	4	5	6	
Informed Consent	X								
Medical History	X								
Physical Exam	X								X
Vital Signs	X	X	X	X	X	X	X	X	X
Clinical Laboratory Tests	X ^b	X ^{b,c}							X ^{b,c}
DISC Interview and Comorbid Disorders Checklist	X								
Administer medication		X	X	X	X	X	X	X	X
SKAMP rating ^d		X	X	X	X	X	X	X	X
PERMP measures ^d		X	X	X	X	X	X	X	X
Side Effect Rating Scale ^e		X	X	X	X	X	X	X	X
Dispense weekly supply of medication		X	X	X	X	X	X	X	
Adverse Medical Experiences	X ^f	X	X	X	X	X	X	X	X
Review compliance			X	X	X	X	X	X	X

^a Or early termination. If a subject did not return to the classroom, the investigator made every effort to see the subject to complete all safety assessments (physical examination, laboratory testing, Side Effect Rating Scale, vital signs, and inquiry of adverse medical experiences).

^b Laboratory tests included standard chemistry, hematology, electrolytes, urinalysis, and urine pregnancy tests (for females who had experienced menarche).

^c During the practice and makeup sessions, labs included blood samples collected for PK analysis before dosing, and at 0.0, 0.5, 1.5, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0, and 24 hours after dosing.

^d SKAMP and PERMP measures occurred only in the classroom setting, once weekly, on the last day of any treatment period.

^e This scale was completed by the teacher during the classroom session and collected from parents for practice and mid-week assessments.

^f Adverse medical experiences were collected starting at the time informed consent/assent was obtained.

9.1.2 Screening (Visit 1) and Washout Period

During the screening period, the investigator determined the appropriateness of each subject's inclusion in the study. The diagnosis of ADHD was confirmed with the NIMH Diagnostic Interview Schedule for Children-Version 4.0 (DISC-4.0; Shaffer et al., 1996) and the Comorbid Disorders Checklist (Hudziak, 1993).

Subjects and their legal guardians or caregivers signed an informed assent/consent form at the screening visit (Visit 1). Subjects identified at the screening visit as eligible candidates were scheduled to participate in 7 additional visits to take place in a laboratory classroom over the next 7 consecutive Saturdays. Study procedures were explained in detail at the screening visit, and the subject's prior dose and regimen of stimulant medication was recorded. Subjects took an 8-minute math pretest to determine the appropriate level of difficulty for the math tests that were to be administered in the classroom sessions. The subject's current stimulant treatment was then discontinued for a washout period of at least 1 week.

9.1.3 Practice Visit (Visit 2)

A practice visit (Visit 2) scheduled for the Saturday following the washout period allowed subjects to become acquainted with the study staff and actual classroom procedures. All subjects were given 1 dose of SLI381 20 mg on the morning of the practice day; and blood samples were collected for PK analysis immediately before dosing, at 0.5, 1.5, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, and 12.0 hours, and at 24 hours (next day, Sunday) post dose. Multiple safety and practice objective and subjective measures were conducted throughout the classroom day. For the purpose of practice, the Swanson, Kotkin, Agler, M-Flynn, and Pelham rating scale (SKAMP) and Permanent Product Measure of Performance (PERMP) math test were completed to assess rater characteristics and to correlate with PK parameters. Timing of these efficacy measures throughout the study closely matched the timing of blood draws for PK analysis (at 0.5, 1.5, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours after dosing). Raters were instructed to consistently observe the same children from week to week. Subjects who could not tolerate the 20 mg dose of SLI381 during the practice visit were excluded from double-blind treatment. Meals were served in the classroom at the practice visit and at all subsequent visits. Meals were standardized (i.e., similar quantity and composition) among sites and included breakfast, a mid-morning snack, lunch, an afternoon snack, and dinner.

9.1.4 Double-blind Treatment (Visits 3 – 8)

At the end of the practice visit (after the 24-hour blood draw on Sunday), all subjects who tolerated the 20 mg dose of SLI381 were randomized to double-blind treatment for each of the next 5 weeks. Saturday classes continued for those 5 weeks plus the make-up week. For each week, subjects received one of the 5 treatments, according to the treatment sequence assigned. These 5 treatments were placebo, Adderall® 10 mg, or SLI381 10 mg, 20 mg, or 30 mg. Subjects were instructed to take one dose each day in the morning around breakfast time for the next 6 days, starting on Sunday. On the following Saturday, subjects were asked to come to the laboratory school and participate in the 8 classroom sessions as they did at Visit 2 (see Table 2). The dosing on the visit day (Saturday) occurred in the classroom prior to the start of the procedures for that day.

On each visit day (Saturday), objective (PERMP) and subjective (SKAMP) measures were assessed in the analog classroom setting according to a predetermined schedule developed by Swanson et al. (1998), which can be reviewed in *Section 16, Appendix IIA, Protocol Cover Sheet/Protocol*. Independent raters using the SKAMP (Wigal et al., 1998) assessed 2 factors of classroom behavior (attention and deportment). In addition, subjects completed a series of math problems that were scored to obtain an objective measure of performance on problems attempted (PERMP attempted) and on problems answered correctly (PERMP correct). Both SKAMP and PERMP measures were completed during most 1½-hour classroom cycles (at 0.5, 1.5, 4.5, 6.0, 7.5, 9.0, 10.5 and 12.0 hours after dosing). At the end of the visit day, teachers completed weekly (Saturday) assessments of side effects, using the Teacher Side Effect Rating Scale. During each double-blind treatment week, parents completed similar side effect

assessments once a week, at the end of the day. The parent's assessment was to have been completed on Wednesday if possible, but no earlier than Tuesday and no later than Thursday.

9.1.5 Final Study Visit (Visit 8)

At the final study visit (Visit 8), subjects received either the missed previous treatment, if any, or random duplication of one of the treatments. The final visit included all classroom procedures as well as blood draws for PK analyses, physical examination, recording of vital signs, clinical laboratory tests (including urinalysis and urine pregnancy test for females who had experienced menarche), SKAMP and PERMP assessments, Side Effect Rating Scale, review of compliance, and recording of adverse medical experiences (AMEs).

Blood samples were collected for PK analysis immediately before dosing, at 0.5, 1.5, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, and 12.0 hours, and at 24 hours (next day, Sunday) post dose.

If a subject was discontinued at any time after entering the study, the investigator was to make every effort to see the subject and complete any safety assessments such as physical examination, clinical laboratory tests, Side Effect Rating Scale, vital signs, and inquiries about AMEs.

9.2 Classroom Procedures

Classroom sessions for Visits 2 through 8 were organized in 1½-hour cycles during a 12-hour day. During the practice day (Visit 2), subjects became acquainted with each other, with the study staff, and with the specific schedule and procedures of the classroom.

9.2.1 Recommended Staff

The classroom staff was divided into 4 areas by function: administrative, school, recess, and medical. The following staffing resources were recommended for each site:

- Administrative: investigator and coordinator(s)
- School: 1 teacher and 2 raters
- Recess: 1 lead counselor, 8 other counselors
- Medical: 1 physician, 1 pharmacist, 2 nurses, and 2 technicians

Additionally, 2 phlebotomists were present for Visits 2 and 8.

Each member of the classroom staff had specific roles and responsibilities. The physician performed physical exams, evaluated vital signs, and evaluated AMEs. The coordinator(s) was responsible for the standardization and implementation of classroom activities, which included training the classroom staff, assisting with the removal of disruptive and aggressive students from the classroom, and serving as a substitute for classroom staff in the event of an absence. The teacher developed and prepared materials for each class session, prepared the classroom for each study day, and conducted the class

sessions by instructing the students when to start and stop seatwork activities (including the objective math tests) and academic group games. The raters prepared and arranged their vantage points and materials for each study day, observed student behavior in the classroom, and completed SKAMP rating scales following each classroom session. The recess staff provided enjoyable activities for the group to motivate the subjects to return for subsequent study visits.

9.2.2 Timing and Sequence of Events

Precise timing of activities was essential. Minute-by-minute responsibilities were specified for each staff member to maintain accurate timing of events. All staff members wore watches that were synchronized at the start of the visit day.

A specific sequence of events defined each 1½-hour cycle, which was repeated across the day. A standard cycle included the following segments:

- 10-minute buffer to allow the group to stay on schedule and provide time for preparation for each event
- 20 minutes to conduct a classroom session that included a seatwork assignment (the 10-minute math test)
- 60 minutes for recess

On the day of the practice visit (Visit 2) and final visit (Visit 8), schedules also included collecting blood samples. Some variation in cycles was allowed for meals and other periodic activities (e.g., collection of vitals or physical exams). Outcome measures (SKAMP and PERMP) were obtained during each classroom session as outlined in Table 2.

Blood samples for PK analysis were taken only during Visit 2 (practice visit) and Visit 8 (final visit) immediately before dosing, and at 0.5, 1.5, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0, and 24 hours after dosing using an in-dwelling catheter system.

Prior to blood sample collection, the medical staff obtained blood pressure and heart rate measures. During all double-blind visits, vital signs were taken at the same time intervals (1.5, 4.5, and 7.5 hours after dosing). To facilitate the process of taking blood samples and collecting vital signs, counselors accompanied subjects in the same order to a separate nurses' station at each of the scheduled times. A reward system was used to facilitate insertion of the catheter and ease of blood draws. An independent technician labeled and processed each sample immediately after collection.

Table 2 Schedule of Activities Across the Day

Time	Hr	Cycle	Group 1 Activities
6:45 a.m.			Arrival
7:00 a.m.			Catheter insertion ^a Vitals/PK ^a immediately before dosing, breakfast
7:30 a.m.	0	C1	Dose, Class 1 (blood draw repeated 30 minutes after dosing)
8:00 a.m.			Recess
9:00 a.m.	1.5	C2	Class 2 Vitals/PK ^a
9:30 a.m.			Recess/Snack
10:30 a.m.	3.0	C3 ^b	Recess PK ^a
11:30 a.m.			Extra Recess
12:00 p.m.	4.5	C4	Class 3 Vitals/PK ^a
12:30 p.m.			Lunch
1:30 p.m.	6.0	C5	Class 4 PK ^a
2:00 p.m.			Recess
3:00 p.m.	7.5	C6	Class 5 Vitals/PK ^a
3:30 p.m.			Recess/snack
4:30 p.m.	9.0	C7	Class 6 PK ^a
5:00 p.m.			Recess
6:00 p.m.	10.5	C8	Class 7 PK ^a
6:30 p.m.			Recess/dinner
7:30 p.m.	12.0	C9	Class 8 PK ^a
8:00 p.m.			Dismiss

^a Catheter insertion and samples for PK analysis were completed only at Visit 2 (practice visit) and Visit 8 (makeup visit). Subjects were required to arrive at the clinic at 6:45 a.m. on these days. For all other visits, subjects were to arrive at 7:00 a.m.

^b Efficacy measures were skipped this period to allow for extra recess time. No class time was scheduled during this cycle.

9.2.3 Group Academic Activities

A series of group academic activities were completed in an order balanced over classroom days. These activities were dynamic, interactive, and group-oriented. In contrast with the objective math test requiring individual seatwork, these activities allowed raters to observe a wider range of behaviors. The content of the academic games and the materials used for each game are provided in Appendix A of the study protocol (see Section 16, Appendix IIC).

9.2.4 Recess Activities

During the recess periods, counselors and subjects played group games that varied from week to week. Activities included Charades; I Spy; 20 Questions; Taboo; Win, Lose, or Draw; and Pictionary[®]. Individual games were provided as well and included cards, Legos[®], computer games, and board games. The recess staff conducted arts and crafts activities inside or held recess on an outdoor playground. During some recess periods, meals and snacks were served.

9.3 Choice of Control Groups

The study was designed to evaluate 3 doses of SLI381 capsule formulations (10 mg, 20 mg, and 30 mg), an extended-release product of mixed amphetamine salts, against placebo and Adderall® 10 mg, the immediate-release product of mixed amphetamine salts. The study utilized a crossover design, in which the subject received one of 5 treatments under study for and during a given time period. Therefore, the study did not employ a control group, per se. Instead, each subject acted as his or her own control, with the comparisons being made among the test drug formulations vs. placebo vs. Adderall® 10 mg.

9.4 Selection of Study Population

Subjects aged 6 to 12 years who satisfied DSM-IV criteria diagnosis of ADHD, combined or hyperactive subtypes, who were on a stable regimen and daily dose of Adderall®, dextroamphetamine, or methylphenidate without unacceptable side effects were eligible for participation in the study. Specific entry criteria are detailed below.

9.4.1 Inclusion Criteria

Subjects qualified to enter the double-blind portion of this study if they satisfied all of the following criteria at screening:

INCLUSION CRITERIA

1. Were male or female between 6 and 12 years of age, inclusive.
2. If female and had experienced menarche, had a negative urine pregnancy test at screening, and was using adequate and reliable contraception (e.g., double-barrier method) throughout the trial.
3. Met DSM-IV criteria for primary diagnosis of ADHD (diagnostic code 314.01) combined subtype or predominantly hyperactive-impulsive subtype based on: (1) a psychiatric evaluation which reviewed DSM-IV criteria, and (2) results from selected modules of the computerized parent version of the NIMH DISC-4.0 (Shaffer et al., 1996).
4. Had been receiving stable regimen and total daily dose of stimulants (Adderall®, dextroamphetamine, or methylphenidate) for at least 1 month prior to screening. The subject should not have experienced any unacceptable side effects and must have shown an adequate response to stimulants based on clinical assessment from all the information available.
5. Provided signature of his or her assent and as such was able to understand that he or she could withdraw from the study at any time. In addition, a parent, legal guardian, or caregiver must have supplied informed consent.
6. Had adequate visual and auditory acuity to complete assessments and was capable of understanding and following classroom instructions.
7. Were generally functioning at age-appropriate levels academically.

Source: Section 16, Appendix IIA, Protocol

9.4.2 Exclusion Criteria

Subjects meeting any of the following exclusion criteria prior to entering the double-blind portion of the study were excluded from the study:

EXCLUSION CRITERIA

EXCLUSION CRITERIA

1. Had a comorbid psychiatric diagnosis (such as psychosis, bipolar illness, pervasive developmental disorder, severe obsessive-compulsive disorder, severe depressive disorder, or severe anxiety disorder) or other symptomatic manifestations that, in the opinion of the examining physician, would contraindicate SLI381 treatment or confound efficacy or safety assessments. Comorbid psychiatric diagnosis was to be established by the DISC-4.0 interview and a comorbid diagnosis checklist (Hudziak et al., 1993).
2. Had a history of seizure during the last 2 years (exclusive of febrile seizures), a tic disorder, or a family history of Tourette's disorder.
3. Had a documented history of aggressive behavior serious enough to preclude participation in regular classroom activities.
4. Were taking clonidine or anticonvulsant drugs.
5. Were taking medications that affected blood pressure or heart rate.
6. Were taking other medications that had central nervous system effects or affected performance (such as sedating antihistamines and decongestant sympathomimetics, either oral or topical).
7. Had taken an investigational drug in the last month.
8. Had a history of suspected substance use disorder (excluding nicotine) or lived with someone with a current diagnosed substance use disorder (according to DSM-IV criteria).
9. Had documented adverse reactions, allergies, or intolerance to Adderall®.
10. Had documented history of failure to respond clinically to Adderall®.
11. Had a diagnosis of hyperthyroidism.
12. Had glaucoma.
13. Did not return to the clinic after the screening visit.
14. Had any clinically significant laboratory abnormalities at screening.
15. Had concurrent chronic or acute illness (such as allergic rhinitis or severe cold), disability, or other condition that might have confounded the results of rating tests administered in the study or that might have increased risk to the subject. Similarly, the subject was to be excluded if he or she had any additional condition(s) that in the investigator's opinion would prohibit the subject from completing the study or would cause participation in the study to not be in the best interest of the subject. This included any significant illness or unstable medical condition that could lead to difficulty complying with the protocol.

Source: Section 16, Appendix IIA, Protocol

9.4.3 Diagnostic Criteria

The DISC 4.0 and the Comorbid Disorders Checklist were used as diagnostic tools at screening.

9.4.3.1 DISC-4.0

The DISC-4.0 is a comprehensive, highly structured diagnostic instrument developed for use by trained lay interviewers to ascertain the most common diagnoses defined by the DSM system. The DISC-4.0 elicits DSM-IV criteria for 31 diagnoses that are known to occur in childhood. Questions are answered *yes*, *no*, *sometimes*, or *somewhat*. The entire interview takes approximately 1 hour and is directed based on answers to previous questions. The computerized parent version of the DISC-4.0 was used at the screening visit in this trial. The specific diagnostic modules/sections used included anxiety disorders, miscellaneous disorders, mood disorders, and disruptive behavior disorders. Symptoms of ADHD were assessed both in the present state and prior to treatment with medication. One interviewer from each center was trained to administer the DISC-4.0 prior to initiation of the study.

9.4.3.2 Comorbid Disorders Checklist

The Comorbid Disorders Checklist is a DSM-IV investigator-completed checklist that queries informants (parent, guardian, caregiver, and/or subject) regarding the subject's past and current symptoms of ADHD and the following common comorbid disorders: oppositional defiant disorder, conduct disorder, separation anxiety disorder, mixed anxiety-depressive disorder, major depressive disorder, and manic episode. The Comorbid Disorders Checklist was administered at screening.

9.4.4 Removal of Subjects from Therapy or Assessment

A subject was considered as having completed the study when he or she completed Visit 8, i.e., completed each treatment period. If a subject prematurely discontinued at any time after entering the study, the investigator was to make every effort to see the subject and complete safety assessments, as shown in *Section 9.1.1, Schedule of Assessments*.

An end-of-study CRF page was completed for every subject who received study medication whether or not the subject completed the study. The reason for any early discontinuation was to be indicated on this form and described in the form's comments section. The primary reason for a premature withdrawal was selected from the following standard categories of early termination:

- *Adverse Medical Experience (Adverse Reaction)*: Clinical or laboratory events occurred that, in the medical judgment of the investigator and for the best interest of the subject, were grounds for discontinuation. This included serious and nonserious AMEs regardless of relation to study medication.
- *Death*: The subject died.
- *Withdrawal of Consent*: The subject desired to withdraw from further participation in the study in the absence of a medical need to withdraw determined by the investigator. If the subject gave a reason for this desire, this reason was to be recorded in the case report form (CRF).
- *Protocol Violation*: The subject's findings or conduct failed to meet the protocol entry criteria or failed to adhere to the protocol requirements (e.g., drug noncompliance, failure to return for defined number of visits). The violation necessitated premature termination from the study.
- *Lost to Follow-up*: The subject stopped coming for visits and study personnel were unable to contact the subject even after issuing a certified letter.
- *Other*: The subject was terminated for a reason other than those listed above, such as theft or loss of study drugs, or termination of study by sponsor.

In case of an early termination, information normally collected at the end of the study was to be obtained at the time of subject withdrawal, if possible. Subjects withdrawn from the study were not to be replaced, and withdrawn subjects could not re-enter the study.

9.5 Treatments

9.5.1 Treatments Administered

Treatments included capsules of SLI381 10 mg, SLI381 20 mg, SLI381 30 mg, and Adderall® 10 mg, as well as matching placebo. Study medication was administered once daily in the morning by subject taking 1 capsule orally. Each treatment condition lasted for 1 week.

At the screening visit (Visit 1), the subject's current stimulant treatment was discontinued for a washout period of 1 week. At the practice visit (Visit 2), all subjects were given a single 20 mg dose of SLI381 capsules.

Subjects who tolerated the 20 mg dose at the practice visit were randomized to receive SLI381 10 mg, SLI381 20 mg, SLI381 30 mg, Adderall® 10 mg, or placebo to be administered as a capsule once daily in the morning starting the next day (Sunday). On scheduled Saturday visits, subjects were given their morning dose after their arrival in the classroom. Breakfast was given after arrival at the classroom prior to dosing.

For the first 5 weeks of the double-blind treatment phase, subjects received a different treatment condition until each subject had completed each treatment condition. At the end of the 5-week sequence, subjects continued double-blind treatment for an extra week (i.e., make-up week), which allowed for duplication of one of the 5 treatment conditions. According to the protocol, if the subject missed one of the previous 5 treatment weeks (including the visit day), he/she would have received the first missed treatment condition during this make-up week. If the subject completed the previous 5 treatment weeks, he/she would have received one of the 5 treatment conditions during the make-up week according to a pre-prepared randomization schedule.

TREATMENTS ADMINISTERED

Treatment Designation	Study Medication	Administration Method
A	Placebo	Oral
B	Adderall® 10 mg	Oral
C	SLI381 10 mg	Oral
D	SLI381 20 mg	Oral
E	SLI381 30 mg	Oral

9.5.2 Identity of Study Drug

All study medications (SLI381 capsules, Adderall® capsules, and placebo capsules) were supplied in bottles directly to each site by the sponsor. The site's pharmacist transferred each treatment medication into an individual medication container of 1-week's supply for each subject. Each bottle was identified by lot or batch number, product name, and strength as shown below, and a precautionary statement. The product was also labeled with manufacture date.

IDENTITY OF STUDY DRUG

	SLI381	Placebo	Comparator
Trade name:	None available	Not applicable	Adderall®
Manufacturer:	Shire Laboratories, Inc.	Shire Laboratories, Inc.	Shire Richwood
Dose(s):	10 mg 20 mg 30 mg	Not applicable	10 mg
Route:	Oral	Oral	Oral
Formulation:	Capsule	Capsule	Capsule
Batch No./Lot No.:	10 mg 9F2797 20 mg 9F2702 30 mg 9F2703	GUS00515.06	B4861*
Date of Manufacture:	10 mg June 10, 1999 20 mg June 14, 1999 30 mg June 16, 1999	June 28, 1999	May 1999

* Overencapsulated commercial tablet

9.5.3 Method of Assigning Subjects to Treatments

Two randomization sequences were prepared and used in the study for each site to randomize subjects into the double-blind treatment weeks. One was for the first 5 core weeks of the crossover treatment, and the other was for the make-up week. The former utilized a 5x5 Latin square to determine the treatment sequence of the subject for the first 5 weeks of double-blind treatment. The Latin square had 5 sequences: ABCDE, BCDEA, CDEAB, DEABC, or EABCD, with approximately one-fifth of subjects being randomized to each of the 5 sequences. The latter was a simple randomization procedure.

The randomization schedules were produced by Ingenix Pharmaceutical Services, the CRO contracted to manage the study. The block size was set at 15 for both randomization schedules.

9.5.4 Dose Selection

SLI381 doses of 10 mg, 20 mg, and 30 mg were chosen because they are currently the only available individual dose strengths that are intended to be marketed. It was desirable to prove the efficacy and safety of every strength of SLI381. In addition, the 10 mg, 20 mg, and 30 mg doses of Adderall® are commonly used daily dosages in clinical practice when this medication was prescribed for the management of children with ADHD.

9.5.5 Blinding

Study medication was shipped to each site in bulk. Each site's pharmacist repackaged the study medication as a 1-week supply of 6 capsules per treatment period for each subject based on the subject's randomized treatment sequence provided by Ingenix. The Saturday dose was kept at the clinic to ensure dosing occurred in the classroom. If a subject lost a dose during the week, it was not to be replaced.

Each site was provided with a set of sealed envelopes in which the identity of the medication was printed for each treatment week, for each randomization number. The

envelope was to be opened only if knowledge of the medication was necessary for optimal emergency treatment. A copy of the randomization code was kept by Ingenix in a secure place. No treatment codes were broken during the study.

A master treatment code was kept in a secured place at Ingenix. Post database lock, treatment code was unblinded by the study statistician at Ingenix.

9.5.6 Prior and Concomitant Illnesses and Treatments

9.5.6.1 Prior and Concomitant Illnesses

As this study was conducted in children with ADHD who were otherwise healthy, there should have been no concomitant illnesses at the time of entry into the study. Illnesses worsening, first occurring, or detected during the study were to be documented as AMEs on the CRF.

9.5.6.2 Prior and Concomitant Treatments

Medications taken within 1 month prior to study entry were recorded on the CRF. Any medication taken by or administered to the subject during the course of the study had to have prior approval by the investigator and recorded in the appropriate CRF. The CRF entry included the dose, regimen, route, indication, and dates of use.

All concomitant medications received during the study are listed in *Section 14, Table 11.1.1*. The most common concomitant medication during the study was local anesthetic for catheter insertion or blood draw (50 subjects). Other common concomitant medications taken during the study included ibuprofen (9 subjects), acetaminophen (6 subjects), cold medications (8 subjects), multiple vitamins (6 subjects), and nutritional supplements (5 subjects).

9.5.6.3 Excluded Medications

The concomitant use of the medications listed below was not allowed during the trial:

- Tricyclic antidepressants
- Other amphetamines or pemoline
- Monoamine oxidase inhibitors
- Serotonin reuptake inhibitors
- Neuroleptics
- Benzodiazepines or benzodiazepine derivatives
- Clonidine
- Anticonvulsant medications
- Cough/cold preparations containing stimulants
- Sedating antihistamines
- Other investigational medications

9.5.7 Treatment Compliance

For the non-classroom days of each treatment week, treatment medications were dispensed in medication containers, which were returned at next visit. Treatment compliance was assessed by capsule counts. Compliance was defined as number of capsules taken divided by number of capsules prescribed multiplied by 100%. Non-compliance was defined as taking less than 80% of study medication during any outpatient evaluation period (visit to visit). Discontinuation for non-compliance was at the investigator's discretion and was noted on the appropriate CRF.

For the classroom day of each treatment week, the subject was administered the scheduled dose in the morning around 7:30 a.m. at the classroom by the study staff.

9.5.8 Drug Accountability

Study drug was shipped in bulk to each site by the sponsor and stored in a locked, limited access area. Each site was responsible for maintenance of cumulative study drug inventory and dispensing records. At the conclusion of the trial, all unused supplies were returned to the sponsor.

9.6 Efficacy and Safety Variables

9.6.1 Efficacy Measures

The primary efficacy measures used in this study included the SKAMP Rating Scale and the PERMP Derived Measures.

The SKAMP is designed for independent observers to rate 13 items with 8 core items to measure children's classroom behaviors. Each item is rated on a 7-point impairment scale: normal (0), slight (1), mild (2), moderate (3), severe (4), very severe (5), or maximal impairment (6). The 8 core items represent attention (items #1 through #4: getting started, sticking with tasks, attending to topic, and stopping for transition) and deportment (items #5 through #8: interacting with students, interacting with staff, remaining quiet, and remaining seated). The outcome score is defined by the average rating score per item, calculated by averaging the scores obtained for the corresponding items for attention and deportment, respectively. The scale can be used to assess multiple ratings taken within a day (Swanson et al., 1998).

To keep track of multiple assessments to be completed at the end of a classroom cycle by a single rater without having to rely on memory, an observation code sheet serves to note behaviors during the session. Codes on the observation sheet are linked to items on the SKAMP and are written next to the appropriate category title (e.g., an *i* for interruption would be written next to school rules).

A detailed description about the SKAMP scale and its coding system is given in Appendix B of the study protocol in *Section 16, Appendix IIA*.

The PERMP measures a subject's performance using a 10-minute written math test performed as seatwork in the classroom. Subjects are given 4 pages of 100 math problems appropriate to their age, and are instructed to work at their desks and to complete as many problems as possible in 10 minutes. Performance is measured by using the number of problems worked correctly and number of problems attempted by the subject within the time limit. Examples of the PERMP items are provided in Appendix E of the study protocol in *Section 16, Appendix IIA*.

Different versions of the PERMP were used among the subjects in this study to adjust for age and ability as determined by the math pretest administered at screening. In addition, different versions were used across classroom cycles and visits in this study, so that a subject did not take the same test more than once. A stopwatch was used to time the test.

9.6.2 Pharmacokinetic Parameters

Blood samples for PK analysis were taken during Visit 2 (practice visit) and Visit 8 (final visit) immediately before dosing, and at 0.5, 1.5, 3.0, 4.5, 6.0, 7.5, 9.0, 10.5, 12.0, and 24 hours post dose. Concentrations of d- and l-amphetamine in plasma were measured by liquid chromatography-mass spectrography at the sponsor's lab. The following PK parameters were calculated for both the single dose administration and at steady state:

Parameter	Description
AUC_{0-24}	Area under the drug concentration-time profile from time 0 to the last data point
AUC_{0-inf} (single dose only)	Area under the drug concentration-time profile from time 0 to infinity
C_{max}	Maximum drug concentration
T_{max}	Time to maximum drug concentration

Complete details of the assay method and calculation method are provided in *Section 16, Appendix VIB: Pharmacokinetical Analytical Report/Technical Report*.

9.6.3 Safety Evaluations

9.6.3.1 Adverse Medical Experiences (AMEs)

An AME was defined as any adverse change from the subject's baseline (pretreatment) condition, including intercurrent illness or laboratory abnormality, that occurred during the study, whether considered related to the investigational treatment or not. AMEs were collected throughout the study beginning at the time informed consent/assent was obtained. Investigators queried for all AMEs in a semi-structured interview format. All AMEs were recorded on the subject's CRF. In addition, side effects noted on the Side Effect Rating Scale were considered AMEs and were recorded as such in the AME section of the CRF. For all AMEs, the investigator pursued and obtained adequate information to determine the outcome of the AME and to assess whether it met the criteria for classification as a serious adverse event (SAE) requiring immediate notification to the sponsor. Follow-up of the AME, even after the date of therapy

discontinuation, was required until the event resolved or stabilized at a level acceptable to the investigator.

All AMEs (including side effects noted on the Side Effect Rating Scale) were recorded in standard terminology rather than the subject's own words. Each AME was evaluated for duration, intensity, and association with the study medication and other causes (additional review was conducted by the Ingenix medical monitor). The action taken and the outcome were also recorded. The intensity of the AME was characterized as mild, moderate, or severe using the following criteria:

- **Mild** events were usually transient and easily tolerated, requiring no special treatment and causing no disruption of the subject's normal daily activities.
- **Moderate** events introduced a low level of inconvenience or concern to the subject and might have interfered with daily activities, but were usually improved by simple therapeutic measures. Moderate experiences might have caused some interference with functioning.
- **Severe** events interrupted the subject's normal daily activities and generally required systemic drug therapy or other treatment. They were usually incapacitating.

When changes in the intensity of an AME occurred more frequently than once a day, the maximum intensity for the experience was noted. If the intensity category changed over a number of days, these changes were recorded separately (with distinct onset dates).

The relationship or association of the study medication in causing or contributing to the AME was characterized as one of the following:

- **Not Related**
- **Possible** suggested that the association of the AME with the study drug was unknown. However, the AME was not reasonably supported by other conditions.
- **Related** suggested that a causal relationship existed between the study drug and the AME, and other conditions (concomitant illness, progression or expression of the disease state, reaction to concomitant medication) did not appear to explain the AME.

Any serious or unexpected AME, including death due to any cause that occurred during the investigation, whether or not related to the study medication, was to be reported within 24 hours. An unexpected AME was one that was not identified in nature, intensity, or frequency in the Investigator's Brochure. The AME was defined as an SAE if it resulted in any of the following outcomes:

- death
- a life-threatening AME

- a persistent or significant disability/incapacity
- inpatient hospitalization (overnight) or prolongation of existing hospitalization
- a congenital anomaly/birth defect

Important medical events that did not result in death, were not life-threatening, or did not require hospitalization could have been considered SAEs when, based upon appropriate medical judgment, they jeopardized the patient and might have required medical or surgical intervention to prevent one of the outcomes listed in this definition. Examples of such events included allergic bronchospasm requiring intensive treatment in an emergency room or at home, blood dyscrasia or convulsions that did not result in an inpatient hospitalization, or the development of drug dependency or drug abuse. A death occurring during the study within 4 weeks of stopping the treatment was to be reported, whether considered treatment-related or not.

A preliminary report on each SAE was to be sent to the study monitor, who forwarded a copy to the sponsor. Such preliminary reports were followed by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents when requested and applicable.

9.6.3.2 Physical Examination

Physical examinations were performed as indicated by the schedule of assessments. The examination included a neurologic evaluation and examination of the skin, heart, lungs, abdomen, and lymph nodes. Height and weight were also recorded. An AME was recorded for any change identified as clinically noteworthy.

9.6.3.3 Laboratory Parameters

The following laboratory tests were performed as indicated by the schedule of assessments:

- Hematology: hemoglobin, hematocrit, erythrocytes, leukocytes, platelets, differential neutrophils, lymphocytes, monocytes, eosinophils, basophils
- Chemistry: sodium, potassium, calcium, phosphorus, total protein, glucose, alkaline phosphatase, AST, ALT, total bilirubin, creatinine, albumin
- Urinalysis: osmolality, pH, glucose, protein, WBC, casts
- Other: urine pregnancy test (for females who had experienced menarche)

A central laboratory (Quest Diagnostics, formerly SmithKline Beecham) analyzed laboratory tests. In the event of an unexplained clinically noteworthy abnormal laboratory test value, the test was repeated immediately and followed until the test value had returned to the normal range and/or an adequate explanation of the abnormality was found.

9.6.3.4 Vital Signs

Vital signs, including oral temperature, pulse, and sitting blood pressure, were performed at screening. For all other visits, only pulse and sitting blood pressure were measured. The subject's sitting blood pressure was to be measured in the same arm by the same study personnel using the same instrument after the subject had been seated for 3 minutes. Blood pressure and heart rate measurements were to precede, not follow, venipunctures.

9.6.3.5 Side Effect Rating Scale

The Side Effect Rating Scale is a questionnaire designed to assess side effects specific to stimulant treatment. The parent version of the scale rates on a 4-point scale from 0 (no side effects) to 3 (severe side effects) 11 items such as appetite loss, headaches, and motor tics. During the double-blind portion of the study, the same parent or guardian completed the parent version of the scale once a week during the 6 intervening days between clinical visit days. The teacher version of the scale was completed by trained classroom personnel and was identical to the parent version except for the exclusion of 1 item related to sleep. Side effects were reported as AMEs on the CRF. The Side Effect Rating Scale is included in Appendix F of the study protocol in *Section 16, Appendix IIA*.

9.6.4 Appropriateness of Measurements

ADHD is one of the most common childhood mental disorders. Pharmacological and behavioral treatments of ADHD target the behavioral and cognitive symptoms associated with the diagnosis of ADHD. The core clinical symptoms of ADHD involve inattention, impulsiveness, and hyperactivity, which reflect impairments in the domains of functioning that are central to mastery of the major developmental tasks of childhood. A majority of children with ADHD tend to perform poorly in school, often despite normal intelligence, and suffer significant social and emotional impairments in the formation and maintenance of relationships with classmates, peers, parents, and teachers.

The SKAMP and PERMP scales utilized in this study measure children's cognitive and behavioral performances in an analog classroom setting, and provide the assessments for efficacy evaluation. They are standard measurements frequently employed in ADHD studies designed to measure children's behaviors in a classroom setting. The repeated application of these measures during a school day allows the assessment of duration of drug action, in comparison with a control therapy such as placebo.

9.7 Data Quality Assurance

9.7.1 Standardization Procedures

The following steps were taken to ensure accurate, consistent, and complete data:

- Prior to study initiation, pre-study site visits were made to confirm the adequacy of each site and associated study personnel. Study initiation meetings were

subsequently held at each site during which the protocol, CRF, and procedural requirements were reviewed with the investigators and other study personnel.

- An investigators meeting was conducted by Shire and Ingenix during which investigators and subinvestigators discussed and developed a common understanding of the protocol, CRF, and study procedures.
- A central laboratory (Quest Diagnostics) was chosen for analysis of laboratory data in order to ensure consistent analysis of specimens, permit uniform reporting, and minimize variability.

A complete, blank CRF is included in *Section 16, Appendix IIB*.

9.7.2 Monitoring and Auditing

Ingenix monitored the study sites according to ICH GCP guidelines and Shire standard operating procedures. At each monitoring visit, progress of the study was assessed and discussed with the investigator, completed CRFs were checked for completeness and accuracy and were compared to the original patient records and/or source documents, signed informed consent forms were inspected, and study supplies were examined.

Audits were conducted during the study at 2 sites by an independent auditor. Copies of the audit reports are on file at Shire.

9.7.3 Data Management

CRFs retrieved from the investigational site were examined at Ingenix for completeness and accuracy by the Data Management department and for safety by the medical monitor. Any significant discrepancies on the CRFs were clarified with the investigator, with the clinical research associate as liaison.

Data from the CRFs were entered onto a database by trained personnel at Ingenix. BBN/Clintrial[®] was used for data entry and verification and for the update/correction process necessitated by the edit/query process. All data were verified by a double-entry process. Written comments were entered and sight-verified. In addition to double-data entry and visual inspection, data were checked to validate ranges, consistency across data panels, and missing values. Protocol deviations were evaluated for potential impact on study results by Ingenix medical research personnel.

When all queries were answered, a quality control audit was conducted on a sample of CRFs against the database. Once the audit was complete and additional queries were resolved (if needed), the database was locked (after approval by Shire). The locked database was then backed up on computer tape. All associated queries are stored in the Central File of Ingenix.

9.8 Statistical Methods and Determination of Sample Size

9.8.1 Statistical and Analytical Plans

The statistical analyses performed in this study were initially outlined in the study protocol. A detailed statistical analysis plan was developed and approved prior to database lock, which clearly defined subject populations, statistical models, and planned comparisons for efficacy and safety evaluation. Ingenix Biostatistics performed the statistical analyses according to the statistical analysis plan. The statistical analysis plan is provided in *Section 16, Appendix VIA, Detailed Statistical Documentation*.

All statistical analyses were done using SAS® Version 6.12 statistical package.

9.8.1.1 Analysis Populations

The following subject analysis populations were defined in the statistical analysis plan prior to database lock and analyzed in this report:

- Study participants: All subjects who satisfied inclusion/exclusion criteria and enrolled into the study were assessed for drug safety;
- Intent-to-treat (ITT) population: All subjects who randomized into the double-blind portion of the study and had at least one efficacy data point, as defined in Section 9.8.1.2, in the first 5 weeks of double-blind treatment (Visits 3 through 7);
- Per-protocol (PP) population: All randomized subjects who completed the first 5 weeks of double-blind treatment (Visits 3 through 7).

Data from the ITT population were used for the primary efficacy analysis. The efficacy data from PP population were also used to provide supportive evidence for the primary efficacy analysis. The study participants population was used for all safety summaries.

9.8.1.2 Analysis of Efficacy Endpoints

The primary efficacy analysis was to compare SKAMP (attention, deportment) and PERMP (attempted, correct) scores among active treatments (including SLI381 doses and Adderall®) vs. placebo. Comparison of SLI381 vs. Adderall® was of secondary importance.

The primary efficacy analysis was carried out using a mixed-effects model of analysis of variance for the ITT population. The term of subject nested within site was considered a random effect in the model. Fixed effects included treatment, period, session, and the treatment-by-session interaction. The overall treatment effect (averaged across the 8 scores observed on the classroom day) was tested first for significance.

Based on the results of the ANOVA, planned pairwise comparisons of each of the active treatments (including SLI381 doses and Adderall®) vs. placebo were further performed within each classroom session, using the method of linear contrasts (equivalent to multiple t-tests). The pattern or profile of the significant differences along the time

domain as disclosed by these planned comparisons would indicate the onset and duration of drug effectiveness during an analog school day, which lasted 12 hours.

In addition, placebo-adjusted SKAMP and PERMP scores were analyzed, using one-sample t-test against a mean value of zero, to further evaluate, with reference to placebo, the onset and duration of drug effectiveness during an analog school day. The placebo-adjusted scores were calculated by subtracting placebo scores from their corresponding treatment scores for each session.

The analyses for the SKAMP and PERMP scores described above were also carried out for the PP population to provide further evidence of treatment efficacy.

9.8.1.3 Pharmacokinetic Analysis

Pharmacokinetic parameters following a single dose of SLI381 20 mg were calculated from the practice visit plasma drug concentrations. Steady state pharmacokinetic parameters after daily administration of study medication (including placebo) for 7 days were calculated from the final visit plasma drug concentrations. These parameters included the following:

C_{max}	Maximum drug concentration
AUC_{0-24}	Area under the concentration-time profile from time 0 to the last data point
AUC_{0-inf} (single dose only)	Area under the drug concentration-time profile from time 0 to infinity
T_{max}	Time to maximum drug concentration

Descriptive statistics and mean drug concentration-time plots were provided for these parameters for single dose and steady state, respectively, and by treatment, where applicable. The PK parameters at steady state were analyzed for treatment differences using 1-way ANOVA with treatment as the factor. Statistical significance was defined at the 5% level. In addition, 2-sample t-test was utilized to compare plasma drug concentrations for SLI381 10 mg vs. Adderall® 10 mg at each sampling time point.

All the analyses described above were carried out for d-amphetamine and l-amphetamine separately.

9.8.1.4 Analysis of PK/PD Relationship

The pharmacokinetic/pharmacodynamic (PK/PD) relationship was analyzed visually by plotting the corresponding PD data obtained during Visit 8 in the same graph with the steady state plasma drug concentration data for each treatment. PK/PD correlation was assessed using Pearson correlation coefficients of blood levels with SKAMP and PERMP scores, respectively, for each patient. Descriptive statistics were reported on the correlation coefficients for each treatment and the 95% confidence interval of the mean correlation was also presented.

All the analyses described above were carried out for d-amphetamine and l-amphetamine separately.

9.8.1.5 Analyses of Safety Data

Extent of Exposure

The exposure of subjects to active drug during the double-blind treatment phase was expressed for each treatment dose in terms of exposure duration, which was categorized as the following: 0 days, 1 day, 2-3 days, 4-7 days, and 8-14 days.

Exposure to study drug was also reported for male and female subgroups.

Early Termination

Subjects terminated from the study were listed in detail, including the treatment they were receiving when the termination occurred and prior treatments they have received.

Adverse Medical Experiences

AMEs were coded using COSTART V dictionary terminology. AMEs were assigned to the treatment that the patient was receiving when the event occurred. AMEs with missing/incomplete start dates were assigned to the first scheduled treatment unless there was proof to the contrary. AMEs were counted only once for each COSTART V body system and preferred term for all incidence tables.

The number (and percent) of subjects experiencing AMEs post dosing or post randomization were summarized within each COSTART V body system, preferred term, and treatment for events at least possibly related to the study medication, and for SAEs. If a severity was missing, the AME was considered moderate. If a relationship was missing, the AME was considered possibly related to the study medication.

A listing was provided for all subjects who discontinued due to an AME.

Side Effect Rating Scale

Descriptive statistics by treatment were presented for both the Parent and Teacher Side Effect Rating Scales, which were observed once weekly during the core randomization treatment weeks (Visits 3 through 7).

Laboratory Tests

Descriptive statistics were reported for the laboratory tests at each assessment point, and changes in laboratory test values from baseline (Visit 2) to the end of the study (Visit 8) were also presented. A listing was presented for abnormal laboratory values noted at the end of the study.

Vital Signs

Descriptive statistics were presented by treatment and the time (hour) after dosing for the observed values.

Physical Examination

The number of subjects with clinically significant changes from screening to the end of the study were tabulated. A listing was provided of all subjects with clinically significant changes.

Medical History

The number of subjects with medical abnormalities noted in the medical history was tabulated by body system. A listing of the subjects with ongoing medical abnormalities was provided.

9.8.1.6 Other Analyses

Protocol Deviations:

The number of subjects with protocol deviations was tabulated. Protocol deviations included receipt of the wrong treatment or an incorrect dose, failure to satisfy inclusion/exclusion criteria but not discontinued, receipt of an excluded concomitant medication, deviation from the randomization or administration schedule, and deviations permitted by the sponsor.

Concomitant Medication

All concomitant medications received during the study were displayed in a listing. Prior and concomitant medications were summarized using the World Health Organization Data Dictionary coding system. Medication usage was classified as follows:

- Prior medication history, referring to any medication ending prior to the first dose of study medication.
- Concomitant medications ongoing at baseline and continuing into the study treatment phase.
- Concomitant medications begun after the start of dosing. Subjects who were administered the same medication more than once were counted only once for that medication.

9.8.2 Determination of Sample Size

Assuming an effect size of 1.0 for the primary efficacy variables (SKAMP and PERMP measures), a minimum of 5 evaluable subjects for each of the 5 treatment sequences was needed to provide 90% power to detect a statistical difference at an alpha level of 0.05 (2-sided), using a paired t-test.

Given an anticipated 40% attrition rate (dropouts plus subjects who missed a medication condition), a minimum of 9 subjects per treatment sequence (for a total of 45 subjects) needed to be randomized to ensure adequate completion of the study. Because of anticipated variability in center accrual and subject retention, each center was asked to randomize 15 subjects to yield a theoretical study maximum of 60 subjects randomized into the double-blind treatment.

9.9 Changes in the Conduct of the Study or the Planned Analyses

9.9.1 Changes in the Conduct of the Study

The protocol called for the final week of the study to be a makeup week with a separate randomization schedule. This separate randomization was to allow for random duplication of a single treatment condition for subjects who did not miss any treatment conditions. Subjects who had missed a medication condition during the double-blind period were to be given the missed treatment during this extra week. Subjects who had missed more than one medication condition were to be treated with the first condition that was missed during the makeup week.

An operational decision was made to not use the last week as a makeup week for missed treatments due to the low drop-out rate and high number of patients who completed 5 weeks of treatment. Instead, the pre-prepared separate randomization schedule was utilized to assign treatments to subjects for the extra week as if there were no subjects missing any treatments during the 5 core treatments weeks.

No amendment to the protocol was issued for this change since it was considered not representing any additional risk to the subject and did not add any additional procedures to the conduct of the study.

9.9.2 Changes in the Statistical Analysis

No changes were made to the planned analyses, which were described in detail in the statistical analysis plan that was developed and approved prior to study database lock and treatment unblinding. The table below lists the key areas where the analysis methodologies outlined in the protocol were further clarified in the statistical analysis plan.

Table 3 Statistical Analysis Clarifications

Area Clarified	Protocol	Statistical analysis plan	Reasons for clarification
Study populations	<p>Safety analysis: <i>Safety-analyzable:</i> all randomized subjects who had data after the first dose of study drug</p> <p>Efficacy analysis: <i>Completed:</i> those randomized subjects who completed the full duration of double-blind treatment with normal termination. Data from completed subjects only was to comprise the primary dataset.</p>	<p>Safety analysis: <i>Study Participants:</i> Screened patients who were admitted into the study and satisfied inclusion/exclusion criteria (subjects who presented for practice visit, Visit 2)</p> <p>Efficacy analysis: <i>ITT:</i> all randomized subjects who had at least 1 efficacy data point in the first 5 weeks of double-blind treatment (Visits 3 through 7) <i>PP:</i> all randomized subjects who completed the first 5 weeks of double-blind treatment (Visits 3 through 7)</p>	<p>Safety analysis: Data from all study participants should be included for safety evaluation. The population defined in the protocol for safety analysis would have excluded those terminated prior to randomization that occurred after Visit 2.</p> <p>Efficacy analysis: The ITT approach was defined as the primary efficacy population to utilize all efficacy data available for evaluation and to avoid biases caused by early terminations. The PP approach was taken to provide further supportive data for drug efficacy should patients receive the full treatment per protocol.</p>
Primary variable(s)	SKAMP scores	<p>a) SKAMP attention and deportment subscales</p> <p>b) PERMP number attempted and number correct</p>	<p>The PERPM is an objective measurement and provides surrogate measures for children's cognitive process, whereas the SKAMP is a subjective rating scale and provides behavioral-oriented judgments from an adult figure. Both behavior and cognition are important areas for improvement of ADHD symptoms.</p>

Area Clarified	Protocol	Statistical analysis plan	Reasons for clarification
Analytical model	<u>Statistical model:</u> Repeated measures ANOVA	<u>Statistical model:</u> Mixed-effects ANOVA	<u>Statistical model:</u> Mixed-effects model can handle not only data with repeated measures, but also missing data. With this kind of study design, it is the most appropriate parametric method for ITT approach, which may include patients with incomplete data.
	<u>Model effects:</u> Treatment, session, sequence, site, and site-by-treatment	<u>Model effects:</u> Treatment, session, period, and treatment-by-session interaction as the fixed-effects Subject nested within center as random effect	<u>Model effects:</u> As the study intended to evaluate drug efficacy in a time domain in reference to a placebo, the proposed effects for the mixed-effects model were the most appropriate effects with the treatment-by-session interaction being the focus.
	<u>Covariates:</u> Assessments obtained during practice session were to serve as covariates.	<u>Covariates:</u> None	<u>Covariates:</u> This was a crossover design. Using the same baseline data as covariate for 5 periods was not appropriate in the model proposed.
Treatment comparison	<u>Planned pair-wise comparisons:</u> a) SLI381 combined vs. placebo; b) SLI381 30 mg vs. placebo; c) SLI381 20 mg vs. placebo; d) SLI381 10 mg vs. placebo; e) Adderall® 10 mg vs. placebo.	<u>Planned pair-wise comparisons:</u> Each active dose was to be compared to placebo for overall treatment effect. Treatment comparisons were to be done under each session for the following: a) SLI381 30 mg vs. placebo; b) SLI381 20 mg vs. placebo; c) SLI381 10 mg vs. placebo; d) Adderall® 10 mg vs. placebo; e) Each SLI381 dose vs. Adderall® 10 mg.	<u>Planned pair-wise comparisons:</u> Whereas overall treatment effect was the focus, further analysis was accomplished by comparison of each active dose with placebo under each session. This comparison disclosed approximately when the drug effect started to become significant, when it would lose the significance, and whether the significant effect would last throughout the school day and into evening hours.

Area Clarified	Protocol	Statistical analysis plan	Reasons for clarification
	<p>Multiplicity: A closed testing procedure in the order presented above was proposed to handle the issue of multiple means comparisons.</p>	<p>Multiplicity: Significance level was set at $p < 0.05$. No special procedure was proposed to adjust p values.</p>	<p>Multiplicity: All the comparisons were a priori, and were carried out following the overall ANOVA test. Given a significant effect ($p < 0.05$) of treatment and/or treatment-by-session interaction, the overall family-wise error rate was less than 0.05.</p>
Missing data imputation	Missing data for individual assessments (SKAMP and PERMP) were to be replaced by using the average of values from adjacent time points in order to carry out a repeated-measures ANOVA on those subjects who completed all 5 treatments.	None	In terms of model execution, missing data imputation is not needed for the mixed-effects model that was to be employed.

10. SUBJECT GROUPS

10.1 Disposition of Subjects

Fifty-one subjects were enrolled. All of them completed the practice visit and were randomized into the double-blind treatment; 92% (47/51) completed the first 5 weeks of double-blind treatment; and 86% (44/51) completed the final (makeup) week (Week 6). Table 4 below summarizes overall subject disposition. A listing of individual subject disposition is presented in *Section 14, Table 1.2.1*.

Table 4 Subject Disposition

	No. of subjects
Enrolled	51
Randomized	51
Completed	44
Discontinued	7
AME	2
Withdrew consent	1
Lost to follow-up	2
Other ^a	2
Analysis populations	
Efficacy	
ITT ^b	49
PP ^c	47
Safety	51

^a One subject 2-17 could not tolerate study; 1 subject 3-04 experienced menarche.

^b Subjects 1-08 and 3-04 discontinued prior to any efficacy evaluations during the double-blind treatment.

^c Subjects 2-17 and 4-08 discontinued prior to completing the first 5 weeks of double-blind treatment.

Source: *Section 14, Tables 1.2.1 and 2.1.1*

Of the 7 subjects who discontinued prematurely, 2 subjects discontinued due to AMEs; 2 were lost to follow-up; 1 withdrew because he could not tolerate being in the study; 1 withdrew because she experienced menarche; and 1 subject withdrew consent due to having problems at school and at home. Table 5 lists all subjects who prematurely discontinued, the treatment at time of discontinuation, the last study visit, study treatments taken prior to discontinuation, and the reason for discontinuation. A listing of early terminations is also presented in *Section 14, Table 1.2.5*.

Early Termination Subject Narratives

- **Subject 1-08**, a 9-year-old white male diagnosed with ADHD combined subtype, experienced stomach ache while receiving SLI381 20 mg. This event, considered severe in intensity, began on October 23, 1999 (which was the practice visit day when

he was dosed with a single 20 mg dose of SLI381). The subject had AMEs of insomnia (moderate), appetite loss (severe), picking at skin and clothing (mild), and alternate hot and cold flashes (moderate) on the same day. He took his first dose of double-blind medication on October 24, 1999. Medication was stopped that day. All events resolved on October 24, 1999. The subject was discontinued from the study on November 2, 1999. The subject had a medical history of ongoing enuresis since July 1999 and was not taking any concomitant medications at the time of the events. The investigator considered all events possibly related to study drug.

Table 5 Early Terminations

Patient No.	Treatment at time of discontinuation	Last visit	Randomization Scheme	Prior Treatment post randomization	Reason for discontinuation
1-08	SLI381 20 mg	2	DEABCD	None	AME: stomach ache
2-17	SLI381 10 mg	4	ABCDEE	Placebo Adderall® 10 mg	Other: could not tolerate being in study
3-04	SLI381 30 mg	2	DEABCE	SLI381 20 mg	Other: experienced menarche
3-09	SLI381 10 mg	6	DEABCB	SLI381 20 mg SLI381 30 mg Placebo	Lost to follow-up
3-10	SLI381 30 mg	6	ABCDEC	Adderall® 10 mg Placebo Adderall® 10 mg SLI381 10 mg SLI381 20 mg	Lost to follow-up
3-11	Placebo	7	CDEABA	SLI381 10 mg SLI381 20 mg SLI381 30 mg Placebo	AME: agitation
4-08	Placebo	4	DEABCE	Adderall® 10 mg SLI381 20 mg SLI381 30 mg	Withdrawal of consent

A=Placebo, B=Adderall® 10 mg, C=SLI381 10 mg, D=SLI381 20 mg, E=SLI381 30 mg

Source: Section 14, Table 1.2.1; Section 16, Appendix VII, Tables 1.1 and 12.2

- **Subject 2-17**, an 8-year-old Hispanic male diagnosed with ADHD combined subtype, could not tolerate the study and discontinued after Visit 4 while taking SLI381 10 mg. The subject had first taken placebo and then Adderall® 10 mg. During the study, the subject had post randomization AMEs of eye blinking (mild, possibly related) stomach ache (mild, not related), defiance (moderate, not related), tiredness (mild, possibly related), and trouble sleeping (mild, possibly related) while taking placebo and AMEs of appetite loss (mild, possibly related), trouble sleeping (mild, possibly related), noncompliance (moderate, not related), and defiance (moderate, not related) while taking Adderall® 10 mg. All AMEs resolved. The subject had no remarkable medical history and had been taking Ritalin 10 mg bid and Ritalin SR 20 mg qd prior to entering the study.

14, Tables 1.1.1 through 1.1.3. Since this was a crossover study and majority subjects received all treatments, no comparisons among treatments were made for the demographic and baseline variables.

11.3 Measurements of Treatment Compliance

Treatment compliance during the core treatment weeks (first 5 weeks of double-blind treatment) is summarized in *Section 14, Table 1.3.1* for all randomized subjects. Treatment compliance was expressed as the percentage of capsules taken by capsule counts compared to the number that should have been taken.

Most patients were between 80% to 100% treatment-compliant throughout the entire 5-week period. When assessed across treatments, compliance was considered to be good and very similar during the 5-week double-blind period, ranging from 91.7% for SLI381 10 mg to 98.0% for SLI381 30 mg.

Table 6 Summary of Subject Demographic and Baseline Characteristics

Characteristic	Category/Parameter	All patients (N=51)
Gender (number [%] of subjects)	Male (%)	44 (86.3)
	Female (%)	7 (13.7)
Race (number [%] of subjects)	White	25 (49.0)
	Black	8 (15.7)
	Hispanic	12 (23.5)
	Asian/Pacific Islander	3 (5.9)
	Other*	3 (5.9)
Age (yr)	Mean	9.5
	SD	1.9
	Min-Max	6.0 – 12.0
Age distribution (number [%] of subjects)	6-8 yr	18 (35.3)
	9-12 yr	33 (64.7)
Weight (lb)	Mean	83.5
	SD	28.9
	Min-Max	48.0 – 161.0
Height (in)	Mean	54.6
	SD	4.9
	Min-Max	45.5 – 65.2
Diagnosis of ADHD (number [%] of subjects)	Hyperactive	1 (2.0%)
	Combined	50 (98.0%)
Duration of Treatment (yr)	Mean	1.7
	SD	1.7
	Min-Max	0.0 – 5.7
Previous treatment (number [%] of subjects)	Amphetamine only	17 (33.3%)
	Methylphenidate only	30 (58.8)
	None Listed	4 (7.8)

* Includes black and white, black and Hispanic.

Source: Section 14, Tables 1.1.1 through 1.1.3

11.4 Efficacy Results

11.4.1 Primary Efficacy Analysis

The primary efficacy analysis utilized the ITT population and the average score per item for SKAMP attention and deportment and the total score of PERMP number attempted and number correct observed for each subject, under each treatment and each classroom session, during the 5 core double-blind treatment weeks. The analysis was carried out using a mixed-effects ANOVA model for each efficacy measure. The results are reported in sections below.

11.4.1.1 SKAMP Attention

Descriptive statistics of the SKAMP attention scores during the core treatment weeks for the ITT population are presented in *Section 14, Table 2.3.1* and summarized in Table 7. Data listings of individual subjects' SKAMP attention scores are contained in *Section 16, Appendix VII, Table 13.1*.

Mean Scores

Mean SKAMP attention scores during the core treatment weeks (the first 5 weeks of double-blind treatment) decreased (improved) for all SLI381 treatments at 1.5 hours post dose, with the greatest decrease occurring at 4.5 hours post dose for subjects taking SLI381 10 mg and 20 mg, and at 6.0 and 7.5 hours post dose for subjects taking SLI381 30 mg. At 12 hours post dose, the mean SKAMP attention score remained below the score at 0.0 hours for all SLI381 treatments.

Subjects taking Adderall® 10 mg showed a similar pattern of scores, which decreased at 1.5 hours post dose and maintained lower until 9.0 hours post dose. However, the score began to increase after that time and by 12 hours post dose, the score was the same as the score at 0.0 hours.

For subjects taking placebo, in contrast, the mean score increased at 1.5 hours post dose, compared to at 0.0 hours, and remained higher at all time points post dose.

ANOVA

As expected, results of the ANOVA (*Section 14, Table 2.3.3*) show highly significant differences for the treatment effect and the treatment-by-session interaction ($p < 0.0001$). In addition, the main effects of period and session were all highly significant ($p < 0.0001$).

The average score over the 8 sessions of the treatment was 1.51, 1.33, 1.30, 1.18 and 1.02 for placebo, Adderall 10 mg, SLI381 10 mg, 20 mg, and 30 mg, respectively. The differences in the average score were highly significant, when compared to placebo treatment, for SLI381 30 mg ($p < 0.0001$), SLI381 20 mg ($p < 0.0001$), SLI381 10 mg ($p < 0.0001$), and Adderall 10 mg ($p < 0.001$).

Planned Pairwise Mean Comparisons Over the Time Course

Results of the planned pairwise mean comparisons of SKAMP attention scores between active drug and placebo (*Section 14, Table 2.3.4*) indicate statistically significant differences between all doses of SLI381 compared with placebo at various time points. When comparing SLI381 and Adderall® with placebo, there were statistically significant ($p < 0.05$) differences favoring active treatment as follows:

- SLI381 30 mg: at all time points from 1.5 to 12.0 hours post dose;
- SLI381 20 mg: starting at 4.5 hours and continuing to 12.0 hours post dose; and marginal significance was seen at 1.5 hours post dose ($p = 0.0513$);

- SLI381 10 mg: at 4.5, 6.0, 7.5, and 10.5 hours post dose; and marginal significance was seen at 12.0 hours post dose ($p=0.0626$);
- Adderall[®] 10 mg: at 1.5, 4.5, 6.0, and 7.5 hours post dose

When comparing the SLI381 doses with Adderall[®] 10 mg, statistically significant differences in favor of SLI381 were seen at various time points. In particular, significant differences in favor of SLI381 doses were seen at 6.0, 7.5, 9.0, 10.5, and 12.0 hours post dose for SLI381 30 mg, at 9.0, 10.5, and 12.0 hours post dose for SLI381 20 mg, and at 12.0 hours post dose for SLI381 10 mg.

Table 7 Mean Scores (SD) of SKAMP Rating Scale: Attention

Time (hr) post dose	Parameter	Treatment				
		Placebo	Adderall [®] 10 mg	SLI381 10 mg	SLI381 20 mg	SLI381 30 mg
0.0	N	44	44	41	44	41
	Mean	1.18	1.59**	1.55*	1.27	1.38
	SD	0.98	1.21	1.05	1.15	1.08
1.5	N	44	43	42	45	42
	Mean	1.31	0.88**	1.27	1.16	0.98**
	SD	0.83	0.83	0.93	1.09	0.99
4.5	N	44	42	42	44	42
	Mean	1.40	0.92***	1.13*	1.07**	0.90***
	SD	0.95	0.92	0.98	1.09	0.82
6.0	N	44	42	42	45	42
	Mean	1.74	1.26***	1.26***	1.14***	0.74***
	SD	1.01	1.18	1.03	0.99	0.74
7.5	N	44	43	42	45	42
	Mean	1.73	1.22***	1.21***	1.13***	0.74***
	SD	1.01	0.87	0.80	1.05	0.81
9.0	N	44	43	41	45	42
	Mean	1.51	1.55	1.40	1.26**	1.05***
	SD	0.97	1.28	1.02	1.15	1.16
10.5	N	42	42	40	45	41
	Mean	1.74	1.60	1.40**	1.27***	1.23***
	SD	0.87	1.26	1.02	0.88	1.28
12.0	N	42	42	40	44	41
	Mean	1.44	1.59	1.23	1.18**	1.15**
	SD	0.93	1.21	0.96	1.01	1.21

* $p<0.05$ compared with placebo, following mixed-effects ANOVA
** $p<0.01$ compared with placebo, following mixed-effects ANOVA
*** $p<0.001$ compared with placebo, following mixed-effects ANOVA
Source: Section 14, Tables 2.3.1, 2.3.3, and 2.3.4

A graphical representation of the SKAMP attention scores is shown in Figure 1.

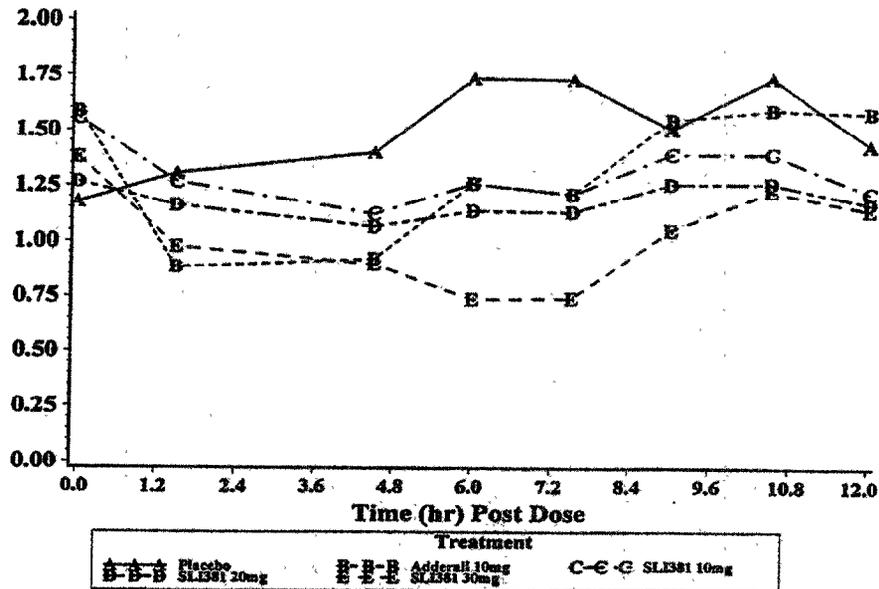


Figure 1 Mean SKAMP Attention Score by Treatment and Classroom Session (ITT)

11.4.1.2 SKAMP Department

Descriptive statistics of SKAMP department scores during the core treatment weeks for the ITT population are presented in *Section 14, Table 2.3.2* and summarized in *Table 8*. Data listings of individual subjects' SKAMP department scores are contained in *Section 16, Appendix VII, Table 13.1*.

Mean Scores

Mean SKAMP department scores during the core treatment weeks (the first 5 weeks of double-blind treatment) decreased (improved) for all SLI381 treatments at 1.5 hours post dose, with the greatest decrease occurring at 4.5 hours post dose for all SLI381 treatments. At 12 hours post dose, the mean SKAMP attention score remained below the score at 0.0 hours for all SLI381 treatments.

For subjects taking Adderall® 10 mg, the mean score was at its lowest 1.5 hours post dose, and it increased beginning at 4.5 hours post dose. However, the mean score was still lower at 12 hours post dose than the score at 0.0 hours.

For subjects taking placebo, in contrast, the mean score increased at 1.5 hours post dose and remained higher than the score at 0.0 hours post dose throughout the day and at 12.0 hours post dose.

Table 8 Mean Scores (SD) of SKAMP Rating Scale: Department

Time (hr) post dose	Parameter	Treatment				
		Placebo	Adderall® 10 mg	SLI381 10 mg	SLI381 20 mg	SLI381 30 mg
0.0	N	44	44	41	44	41
	Mean	1.88	2.43**	2.28	2.26	1.96
	SD	1.39	1.76	1.50	1.37	1.51
1.5	N	44	43	42	45	42
	Mean	2.22	1.08***	1.91	1.69**	1.58***
	SD	1.37	1.27	1.40	1.26	1.58
4.5	N	44	42	42	44	42
	Mean	2.28	1.25***	1.80**	1.22***	0.90***
	SD	1.31	1.26	1.28	1.00	0.89
6.0	N	44	42	42	45	42
	Mean	2.88	1.70***	1.85***	1.84***	1.13***
	SD	1.40	1.64	1.31	1.49	1.19
7.5	N	44	43	42	45	42
	Mean	2.90	1.94***	2.13***	1.67***	1.29***
	SD	1.34	1.414	1.24	1.39	1.34
9.0	N	44	43	41	45	42
	Mean	2.82	2.04***	2.35**	1.79***	1.46***
	SD	1.16	1.46	1.41	1.45	1.33
10.5	N	42	42	40	45	41
	Mean	2.66	2.17*	2.44	2.15**	1.45***
	SD	1.31	1.42	1.52	1.69	1.51
12.0	N	42	42	40	44	41
	Mean	1.99	1.91	2.15	1.73	1.59**
	SD	1.25	1.45	1.32	1.26	1.57

* p<0.05 compared with placebo, following mixed-effects ANOVA
** p<0.01 compared with placebo, following mixed-effects ANOVA
*** p<0.001 compared with placebo, following mixed-effects ANOVA
Source: Section 14, Tables 2.3.2, 2.3.5, and 2.3.6

A graphical representation of the SKAMP department scores is shown in Figure 2.

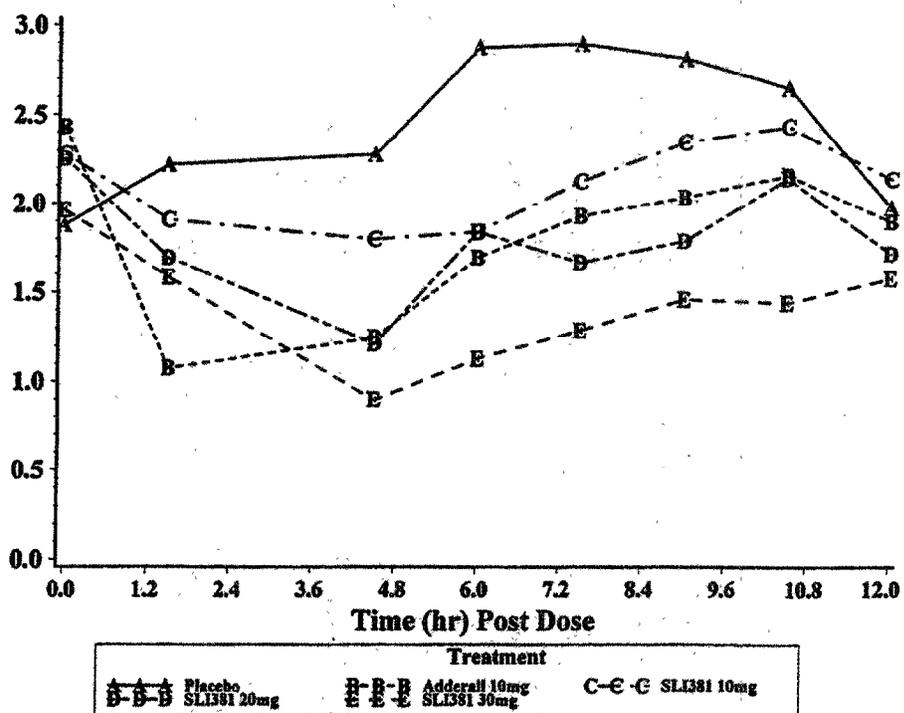


Figure 2 Mean SKAMP Department Score by Treatment and Classroom Session (ITT)

ANOVA

As expected, results of the ANOVA (*Section 14, Table 2.3.5*) show highly significant differences for the treatment effect and treatment-by-session interaction ($p < 0.0001$). In addition, the main effects of period and session were all highly significant ($p < 0.0001$).

The average score over the 8 sessions of the treatment was 2.46, 1.82, 2.11, 1.79 and 1.42 for placebo, Adderall 10 mg, SLI381 10 mg, 20 mg, and 30 mg, respectively. The differences in the average score were highly significant, when compared to placebo treatment, for SLI381 30 mg ($p < 0.0001$), SLI381 20 mg ($p < 0.0001$), SLI381 10 mg ($p < 0.0001$), and Adderall 10 mg ($p < 0.0001$).

Planned Pairwise Mean Comparisons Over the Time Course

Results of the planned pairwise mean comparisons of SKAMP department scores between active drug and placebo (*Section 14, Table 2.3.6*) indicate statistically significant differences between all doses of SLI381 compared with placebo at various time points. When comparing SLI381 and Adderall® with placebo, there were statistically significant ($p < 0.05$) differences favoring active treatments as follows:

- SLI381 30 mg: at all time points from 1.5 to 12.0 hours post dose;

- SLI381 20 mg: at all time points from 1.5 to 10.5 hours; marginal significance was seen at 12.0 hours post dose ($p=0.0531$);
- SLI381 10 mg: at 4.5, 6.0, 7.0, and 9.0 hours post dose; marginal significance was seen at 1.5 hours post dose ($p=0.0725$) and 10.5 hours post dose ($p=0.0724$);
- Adderall® 10 mg: at all time points from 1.5 to 10.5 hours post dose.

When comparing the SLI381 doses with Adderall® 10 mg, statistically significant differences in favor of SLI381 30 mg were seen at various time point. In particular, significant differences were seen at all time points from 4.5 to 12.0 hours post dose for SLI381 30 mg.

11.4.1.3 PERMP Number Attempted

Descriptive statistics of the PERMP number attempted during the core treatment weeks for the ITT population are presented in *Section 14, Table 2.3.7* and summarized in *Table 9*. Data listings of individual subjects' PERMP scores are contained in *Section 16, Appendix VII, Table 14.1*.

Mean Scores

Mean PERMP number attempted during the core treatment weeks (the first 5 weeks of double-blind treatment) increased (improved) for all SLI381 treatments at 1.5 hours post dose, with the greatest increase occurring at post dose hours from 4.5 to 10.5 hours, depending upon the doses. At 12 hours post dose, the mean PERMP number attempted remained above the score at 0.0 hours for all SLI381 treatments.

For subjects taking Adderall® 10 mg, the mean scores increased at 1.5 hours post dose with the peak effect at 4.5 hours post dose and started to decrease afterward.

For subjects taking placebo, the mean scores started to decrease at 4.5 hours post dose and continued the downward trend throughout the day.

ANOVA

As expected, results of the ANOVA (*Section 14, Table 2.3.9*) show highly significant differences for the treatment and treatment-by-session interaction ($p<0.0001$). In addition, the session effect was highly significant ($p<0.0001$), and the period effect was also significant ($p<0.05$).

The average score over the 8 sessions of the treatment was 73.20, 84.63, 86.98, 97.88 and 109.49 for placebo, Adderall 10 mg, SLI381 10 mg, 20 mg, and 30 mg, respectively. The differences in the average score were highly significant, when compared to placebo treatment, for SLI381 30 mg ($p<0.0001$), SLI381 20 mg ($p<0.0001$), SLI381 10 mg ($p<0.0001$), and Adderall 10 mg ($p<0.001$).

Planned Pairwise Mean Comparisons Over the Time Course

Results of the planned pairwise mean comparisons of PERMP number attempted scores between active drug and placebo (*Section 14, Table 2.3.10*) indicate statistically significant differences between all doses of SLI381 and placebo at various time points. When comparing SLI381 and Adderall® with placebo, there were statistically significant ($p < 0.05$) differences favoring active treatments as follows:

- SLI381 30 mg: at all time points from 1.5 to 12.0 hours post dose;
- SLI381 20 mg: at all time points from 1.5 to 12.0 hours post dose;
- SLI381 10 mg: at all time points from 4.5 to 10.5 hours post dose;
- Adderall® 10 mg: at 1.5, 6.0, 7.5 and 9.0 hours post dose.

Table 9 Mean Scores (SD) of PERMP Rating Scale: Number Attempted

Time (hr) post dose	Parameter	Treatment				
		Placebo	Adderall® 10 mg	SLI381 10 mg	SLI381 20 mg	SLI381 30 mg
0.0	N	44	41	41	44	41
	Mean	89.43	59.37***	63.71**	68.36*	80.39
	SD	56.22	38.43	45.38	46.39	53.56
1.5	N	44	43	42	45	42
	Mean	88.61	118.86***	102.62	102.87*	110.98**
	SD	58.24	65.04	58.45	61.16	52.28
4.5	N	44	42	42	44	42
	Mean	85.61	100.21	106.12*	111.48***	131.29***
	SD	64.94	56.71	63.86	62.65	56.21
6.0	N	44	42	42	45	42
	Mean	69.16	95.83**	102.62***	120.87***	127.90***
	SD	49.28	62.00	60.22	64.50	61.68
7.5	N	44	43	41	45	42
	Mean	60.39	81.16*	87.85**	107.87***	120.12***
	SD	42.87	52.51	57.54	65.57	60.74
9.0	N	44	42	41	45	42
	Mean	60.18	84.40**	79.80*	89.27***	108.19***
	SD	46.92	59.88	50.22	55.67	62.27
10.5	N	42	42	40	45	41
	Mean	58.05	62.21	78.95*	90.07***	100.20***
	SD	41.79	51.93	49.38	50.61	54.12
12.0	N	42	41	40	44	41
	Mean	73.48	73.37	72.43	91.77**	95.63**
	SD	51.94	49.48	44.76	59.36	54.89

* $p < 0.05$ compared with placebo, following mixed-effects ANOVA
 ** $p < 0.01$ compared with placebo, following mixed-effects ANOVA
 *** $p < 0.001$ compared with placebo, following mixed-effects ANOVA
 Source: Section 14, Tables 2.3.7, 2.3.9, and 2.3.10

A graphical representation of the PERMP number attempted is shown in Figure 3.

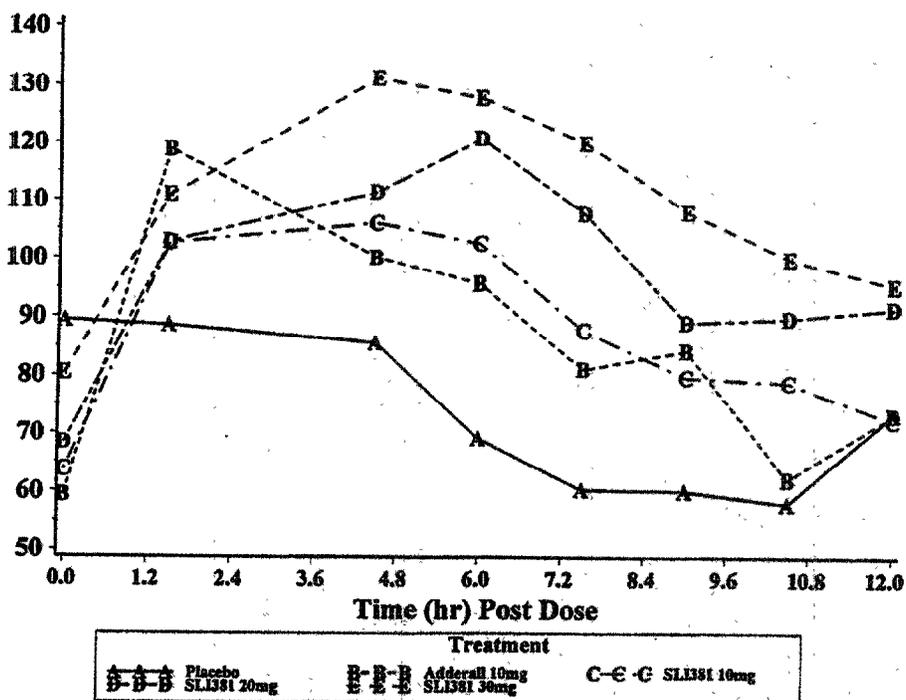


Figure 3 Mean PERMP Number Attempted by Treatment and Classroom Session (ITT)

When comparing the SLI381 doses with Adderall® 10 mg, statistically significant differences in favor of SLI381 were seen at various time points. In particular, significant differences favoring of SLI381 were seen at all time points from 4.5 to 12.0 hours post dose for SLI381 30 mg; at 6.0, 7.5, 10.5, and 12.0 hours post for SLI381 20 mg; and at 10.5 hours post dose for SLI381 10 mg.

11.4.1.4 PERMP Number Correct

Descriptive statistics of the PERMP number correct during the core treatment weeks for the ITT population are presented in Section 14, Table 2.3.8 and summarized in Table 10. Data listings of individual subjects' PERMP scores are contained in Section 16, Appendix VII, Table 14.1.

Mean Scores

Mean PERMP number correct during the core treatment weeks (the first 5 weeks of double-blind treatment) increased (improved) for all SLI381 treatments at 1.5 hours post dose, with the greatest increase occurring at post dose hours from 1.5 to 9.0 hours, depending upon doses. At 12 hours post dose, the mean PERMP number correct remained above the score at 0.0 hours for all SLI381 treatments.

For subjects taking Adderall® 10 mg, the mean number correct peaked at 1.5 hours and then started to decrease afterward. However, it still remained higher at the end of the day than at the beginning of the day.

For subjects taking placebo, in contrast, the mean number correct started to decrease at 4.5 hours post dose and continued to its downward trend throughout the day.

Table 10 Mean Scores (SD) of PERMP Rating Scale: Number Correct

Time (hr) post dose	Parameter	Treatment				
		Placebo	Adderall® 10 mg	SLI381 10 mg	SLI381 20 mg	SLI381 30 mg
0.0	N	44	41	41	44	41
	Mean	86.77	56.20***	60.95***	65.39*	77.78
	SD	56.09	38.02	44.30	45.96	52.45
1.5	N	44	43	42	45	42
	Mean	85.20	112.72***	97.74	98.11*	105.52**
	SD	58.46	68.89	59.85	61.27	54.72
4.5	N	44	42	42	44	42
	Mean	77.77	94.69*	102.12**	107.18***	123.79***
	SD	51.06	59.06	62.34	61.91	55.70
6.0	N	44	42	42	45	42
	Mean	63.23	90.29***	97.90***	112.49***	124.52***
	SD	44.31	63.84	60.32	67.94	61.14
7.5	N	44	43	41	45	42
	Mean	57.34	72.58	82.12**	103.80***	115.55***
	SD	43.25	54.47	57.40	64.50	60.62
9.0	N	44	42	41	45	42
	Mean	54.23	73.40*	74.44*	85.64***	105.02***
	SD	46.02	53.30	48.90	55.55	61.38
10.5	N	42	42	40	45	41
	Mean	50.17	60.40	73.55**	86.16***	97.39***
	SD	40.02	51.42	48.59	50.86	53.60
12.0	N	42	41	40	44	41
	Mean	64.88	67.78	68.85	87.25***	92.54***
	SD	50.30	48.00	45.11	60.72	54.30

* p<0.05 compared with placebo, following mixed-effects ANOVA
** p<0.01 compared with placebo, following mixed-effects ANOVA
*** p<0.001 compared with placebo, following mixed-effects ANOVA
Source: Section 14, Tables 2.3.8, 2.3.11, and 2.3.12

A graphical representation of the PERMP number correct is shown in Figure 3.

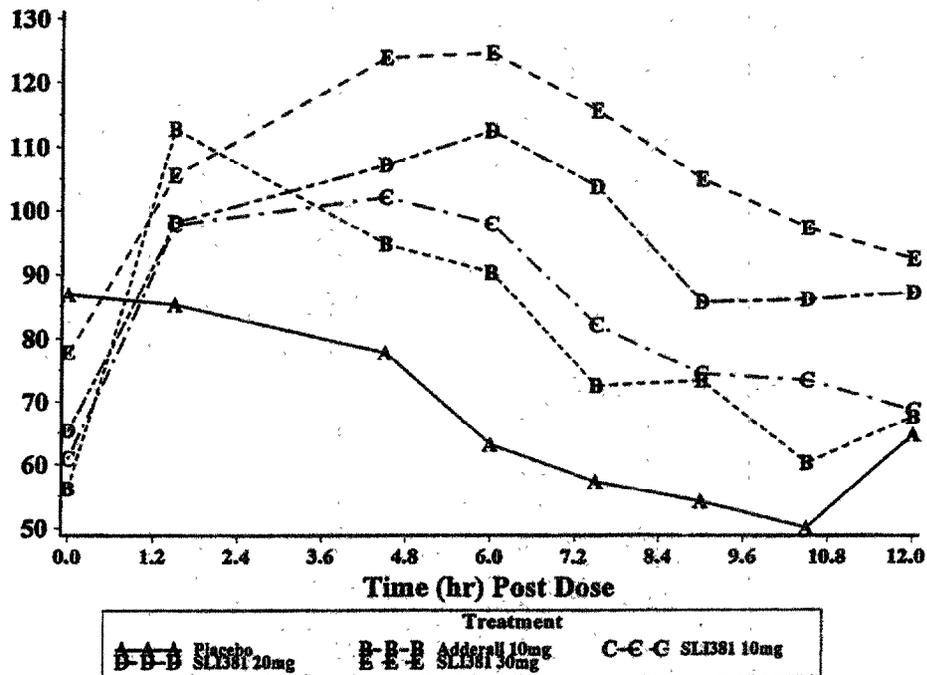


Figure 4 Mean PERMP Number Correct by Treatment and Classroom Session (ITT)

ANOVA

As expected, results of the ANOVA (Section 14, Table 2.3.11) show highly significant differences for the treatment effect and treatment-by-session interaction ($p < 0.0001$). In addition, the session effect was highly significant ($p < 0.0001$), and the period effect was also significant ($p < 0.05$).

The average score over the 8 sessions of the treatment was 67.56, 78.69, 82.43, 93.31 and 105.41 for placebo, Adderall 10 mg, SLI381 10 mg, 20 mg, and 30 mg, respectively. The differences in the average score were highly significant, when compared to placebo treatment, for SLI381 30 mg ($p < 0.0001$), SLI381 20 mg ($p < 0.0001$), SLI381 10 mg ($p < 0.0001$), and Adderall 10 mg ($p < 0.001$).

Planned Pairwise Mean Comparisons Over the Time Course

Results of the planned pairwise mean comparisons of PERMP number correct scores between active drug and placebo (Section 14, Table 2.3.12) indicate statistically significant differences between all doses of SLI381 and placebo at various time points. When comparing SLI381 and Adderall® with placebo, there were statistically significant ($p < 0.05$) differences favoring active treatments as follows:

- SLI381 30 mg: at all time points from 1.5 to 12.0 hours post dose;
- SLI381 20 mg: at all time points from 1.5 to 12.0 hours post dose;

- SLI381 10 mg: at all time points from 4.5 to 10.5 hours post dose;
- Adderall® 10 mg: at 1.5, 4.5, 6.0, and 9.0 hours post dose; marginal significance was seen at 7.5 hours post dose.

When comparing the SLI381 doses with Adderall® 10 mg, statistically significant differences in favor of SLI381 were seen at various time points. In particular, significant differences favoring SLI381 were seen at all time points from 4.5 to 12.0 hours post dose for SLI381 30mg, at all time points from 6.0 to 12.0 hours post dose for SLI381 20 mg, and at 10.5 hours post dose for SLI381 10 mg.

11.4.2 Secondary Efficacy Analyses

The secondary efficacy analysis involved the same analyses performed for the primary efficacy analysis, with the exception that it was performed for the PP population.

11.4.2.1 SKAMP Scores

Descriptive statistics of the SKAMP attention and deportment scores during the core treatment weeks for the PP population are presented in *Section 14, Table 2.4.1* and *Table 2.4.2*, respectively. Data listings of individual subjects' SKAMP scores are contained in *Section 16, Appendix VII, Table 13.1*.

Mean Scores

SKAMP attention score results for the PP population were similar to those of the ITT population. The mean attention score during the core treatment weeks (the first 5 weeks of double-blind treatment) decreased at 1.5 hours post dose, with the greatest decrease occurring at 4.5 hours post dose for subjects taking SLI381 10 mg and subjects taking SLI381 20 mg and at 7.5 hours post dose for subjects taking SLI381 30 mg. At 12 hours post dose, the mean SKAMP attention score remained below the score at 0.0 hours for all SLI381 treatments. The mean score increased for subjects taking placebo at 1.5 hours post dose and remained higher throughout the day and at 12.0 hours post dose. Subjects taking Adderall® 10 mg had decreased scores at 1.5 hours post dose, but scores began to increase at 4.5 hours post dose; at 12 hours post dose, the score was slightly higher than the score at 0.0 hours.

SKAMP deportment score results for the PP population were also similar to those of the ITT population. The mean deportment score during the core treatment weeks (the first 5 weeks of double-blind treatment) decreased at 1.5 hours post dose, with the greatest decrease occurring at 4.5 hours post dose for subjects taking SLI381 treatments. At 12 hours post dose, the mean SKAMP deportment score remained below the score at 0.0 hours for all SLI381 treatments. The mean score increased for subjects taking placebo at 1.5 hours post dose and remained higher throughout the day and at 12.0 hours post dose. Subjects taking Adderall® 10 mg had decreased scores at 1.5 hours post dose, but scores

began to increase at 4.5 hours post dose; at 12 hours post dose, the score was lower than the score at 0.0 hours.

ANOVA

The results of the ANOVA (*Section 14, Table 2.4.3 and Table 2.4.5*) for PP population were similar to those of ITT population, showing highly significant treatment-by-session interaction ($p < 0.0001$) for SKAMP attention and department. In addition, the main effects of treatment, period, and session were all highly significant ($p < 0.0001$) for both attention and department.

Planned Pairwise Mean Comparisons

Results of the planned pairwise mean comparisons of SKAMP attention and department scores between active drug and placebo (*Section 14, Table 2.4.4 and 2.4.6*) indicate statistically significant differences ($p < 0.05$) between both SLI381 20 and 30 mg vs. placebo starting at 1.5 hours post dose and continuing throughout the day until 12.0 hours post dose for SKAMP attention and department. Significant differences ($p < 0.05$) between SLI381 10 mg and placebo were seen at 4.5, 6.0, 7.5, and 10.5 hours post dose, with marginal significance at 12.0 hours post dose for attention, and from 4.5 to 9.0 hours post dose for department. Significant differences ($p < 0.05$) between Adderall® 10 mg and placebo were seen from 1.5 to 7.5 hours post dose for attention and from 1.5 to 10.5 hours post dose for department.

When comparing the SLI381 doses with Adderall® 10 mg, statistically significant differences in favor of SLI381 were seen at various time points. In particular, significant differences favoring SLI381 were seen starting from 4.5 to 6.0 hours post dose throughout the rest of the day for SLI381 30 mg. For SLI381 20 mg vs. Adderall® 10 mg, significant differences were seen at 9.0, 10.5, and 12.0 hours post dose for attention. Compared to SLI381 10 mg, Adderall® 10 mg showed lower scores ($p < 0.05$) at 1.5 hours post dose for attention, and at 1.5 and 4.5 hours post dose for department, which were however consistent with the drug composition of SLI381 10 mg that has 50:50 drug substance for immediate release vs. delayed release pellets.

11.4.2.2 PERMP Scores

Descriptive statistics of the PERMP number attempted and number correct during the core treatment weeks for the PP population are presented in *Section 14, Table 2.4.7 and Table 2.4.8*, respectively. Data listings of individual subjects' PERMP scores are contained in *Section 16, Appendix VII, Table 14.1*.

Mean Scores

PERMP number attempted for the PP population was similar to that of the ITT population. The mean number attempted during the core treatment weeks (the first 5 weeks of double-blind treatment) increased at 1.5 hours post dose, with the greatest

increase occurring at 4.5, 6.0, and 4.5 hours post dose for subjects taking SLI381 10, 20, and 30 mg, respectively. At 12 hours post dose, the mean number attempted remained above the score at 0.0 hours for all SLI381 treatments. The mean decreased for subjects taking placebo at 1.5 hours post dose and remained lower throughout the day and at 12.0 hours post dose. Subjects taking Adderall® 10 mg had increased scores at 1.5 hours post dose, but scores began to decrease at 4.5 hours post dose; at 12 hours post dose, the score was slightly higher than the score at 0.0 hours.

PERMP number correct for the PP population was also similar to that of the ITT population. The mean number correct during the core treatment weeks (the first 5 weeks of double-blind treatment) increased at 1.5 hours post dose, with the greatest increase occurring at 4.5, 6.0, and 6.0 hours post dose for subjects taking SLI381 10, 20, and 30 mg, respectively. At 12 hours post dose, the mean number correct remained above the score at 0.0 hours for all SLI381 treatments. The mean decreased for subjects taking placebo at 1.5 hours post dose and remained lower throughout the day and at 12.0 hours post dose. Subjects taking Adderall® 10 mg had increased scores at 1.5 hours post dose, but scores began to decrease at 4.5 hours post dose; at 12 hours post dose, the score was higher than the score at 0.0 hours.

ANOVA

The results of the ANOVA (*Section 14, Table 2.4.9 and Table 2.4.11*) for the PP population were similar to those of the ITT population, showing highly significant treatment-by-session interaction ($p < 0.0001$) for PERMP number attempted and correct. In addition, the main effects of treatment and session were all highly significant ($p < 0.0001$), and the period effect was also significant ($p < 0.05$).

Planned Pairwise Mean Comparisons

Results of the planned pairwise mean comparisons of PERMP number attempted and number correct between active drug and placebo (*Section 14, Table 2.4.10 and 2.4.12*) indicate statistically significant differences, in favor of active treatments, at all time points from 1.5 to 12.0 hours post dose for the SLI381 30 mg and 20 mg, and at all time points from 4.5 to 10.0 hours post dose for the SLI381 10 mg. Statistically significant differences between Adderall® 10 mg and placebo were seen at 1.5, 6.0, 7.5, and 9.0 hours post dose for number attempted and at 1.5, 4.5, 6.0, and 9.0 hours post dose for number correct.

When comparing the SLI381 doses with Adderall® 10 mg, statistically significant differences in favor of SLI381 were seen at various time points. In particular, significant differences ($p < 0.05$) were seen between SLI381 30 mg and Adderall® 10 mg from 4.5 to 12.0 hours post dose for both measures; and between SLI381 20 mg and Adderall® 10 mg from 4.5 to 12.0 hours post dose for number correct and at 6.0, 7.5, 10.5, and 12.0 hours post dose for number attempted; and between SLI381 10 mg and Adderall® 10 mg at 10.5 hours post dose for both measures.

Final

Date: July 31, 2000

10-6008

11.4.2.3 Placebo-Adjusted Efficacy Scores

Placebo-adjusted SKAMP and PERMP scores were calculated by subtracting placebo scores from their corresponding treatment scores for each classroom session for each treatment during the core treatment weeks for the PP population. The resultant mean scores for SKAMP are presented in *Section 14, Tables 2.5.1 and 2.5.2*. Resultant mean PERMP scores are presented in *Section 15, Tables 2.5.3 and 2.5.4*.

Overall, patterns were similar to the non adjusted scores.

11.4.3 Pharmacokinetic Analysis

11.4.3.1 Plasma Drug Concentration Following A Single 20 mg Dose

Descriptive statistics for the plasma drug concentrations and PK parameters observed following a single dose administration of SLI 381. 20 mg (practice visit) are presented in *Section 14, Tables 3.1.1 and 3.1.2*, respectively. Plasma drug concentration-time plots are presented in *Section 14, Figure 1.1.3*.

Following the administration of a single 20 mg dose of SLI381, the AUC_{0-24} was 703.91 ng.hr/mL for d-isomer and 216.20 ng.hr/mL for l-isomer; the C_{max} was 48.81 ng/mL for d-isomer and 14.80 ng/mL for l-isomer; and the T_{max} was about 7 hours for both isomers. The mean AUC_{0-24} , AUC_{0-inf} , C_{max} , and T_{max} following a single 20 mg dose are summarized in Table 11.

Table 11 AUC_{0-24} , AUC_{0-inf} , C_{max} , and T_{max} Following A Single 20 mg Dose Administration

Measure	Parameter	AUC_{0-24} (ng.hr/mL)	AUC_{0-inf} (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
d-amphetamine	Mean	703.91	936.6	48.81	6.78
	SD	190.25	319.0	13.52	3.19
l-amphetamine	Mean	216.20	309.0	14.80	6.94
	SD	59.50	115.0	4.28	3.28

Source: *Section 14, Table 3.1.2*

11.4.3.2 Plasma Drug Concentration at Steady State

Descriptive statistics for the plasma d-amphetamine concentrations and PK parameters observed at steady state during the extra double-blind week are presented in Tables 3.2.1 and 3.2.2, respectively. Descriptive statistics for the plasma l-amphetamine concentration and PK parameters observed at steady state during the extra double-blind week are presented in Tables 3.2.3 and 3.2.4, respectively. Plasma drug concentration-time plots are presented in *Section 14, Figure 1.1.1 for d-isomer and Figure 1.1.2 for l-isomer*.

For d-amphetamine, following a 1-week administration of once-a-day SLI381 doses or Adderall® 10 mg, the mean AUC_{0-24} was 1364.37 ng.hr/mL, 777.24 ng.hr/mL, and 431.88

ng.hr/mL for SLI381 30 mg, 20 mg, and 10 mg, respectively, compared to 422.51 ng.hr/mL for Adderall® 10 mg. The mean C_{max} was 89.04 ng/mL, 54.63 ng/mL, and 28.82 ng/mL for SLI381 30 mg, 20 mg, and 10 mg, respectively, compared to 33.80 ng/mL for Adderall® 10 mg. The mean T_{max} was 5.50 hr, 5.83 hr, and 6.38 hr for SLI381 30 mg, 20 mg, and 10 mg, respectively, compared to 3.33 hr for Adderall® 10 mg.

For l-amphetamine, following a 1-week administration of once-a-day SLI381 doses or Adderall® 10 mg, the mean AUC_{0-24} was 443.53 ng.hr/mL, 261.63 ng.hr/mL, and 138.34 ng.hr/mL for SLI381 30 mg, 20 mg, and 10 mg, respectively, compared to 142.82 ng.hr/mL for Adderall® 10 mg. The mean C_{max} was 28.08 ng/mL, 17.15 ng/mL, and 8.82 ng/mL for SLI381 30 mg, 20 mg, and 10 mg, respectively, compared to 10.64 ng/mL for Adderall® 10 mg. The mean T_{max} was 5.50 hr, 5.67 hr, and 6.38 hr for SLI381 30 mg, 20 mg, and 10 mg, respectively, compared to 3.22 hr for Adderall® 10 mg.

When adjusted for dose, the mean AUC and C_{max} were similar among the SLI381 doses and Adderall® 10 mg, and the mean T_{max} of SLI381 10 mg was 3 hours longer than that of Adderall® 10 mg.

Table 12 provides descriptive statistics for d- and l-amphetamine at steady state during the final week of the study.

Table 12 AUC_{0-24} , C_{max} , and T_{max} at Steady State During Final Week

Parameter Treatment	Measure	AUC_{0-24} (ng.hr/mL)	C_{max} (ng/mL)	T_{max} (hr)
d-amphetamine				
SLI381 30 mg (n=6)	Mean	1364.37	89.04	5.50
	SD	364.31	15.64	2.05
SLI381 20 mg (n=9)	Mean	777.24	54.63	5.83
	SD	304.32	18.76	1.75
SLI381 10 mg (n=8)	Mean	431.88	28.82	6.38
	SD	123.01	6.18	3.47
Adderall® 10 mg (n=9)	Mean	422.51	33.80	3.33
	SD	138.27	11.07	1.25
l-amphetamine				
SLI381 30 mg (n=6)	Mean	443.53	28.08	5.50
	SD	133.67	6.49	2.05
SLI381 20 mg (n=9)	Mean	261.63	17.15	5.67
	SD	120.15	6.80	2.22
SLI381 10 mg (n=8)	Mean	138.34	8.82	6.38
	SD	40.25	1.85	3.47
Adderall® 10 mg (n=9)	Mean	142.82	10.64	3.22
	SD	46.42	3.49	1.46

Source: Section 14, Table 3.2.2 and 3.2.4

Results of the comparative analysis of the steady state PK parameters are presented in *Section 14, Table 3.2.5*. Results of the comparative analysis of the steady state plasma drug levels between SLI381 10 mg and Adderall® 10 mg are presented in *Section 14, Table 3.2.6*.

11.4.4 Analysis of PK/PD Relationship

The plasma drug concentration-time averages and the scores of efficacy measures obtained at the make-up week are plotted in the same graph in *Section 14, Figures 2.1.1 and 2.1.2*. An analysis of Pearson correlation between plasma drug levels and efficacy measures was carried out. Descriptive statistics of the correlation are presented in *Section 14, Tables 3.3.1 and 3.3.2* and summarized in Table 13 below.

Table 13 Correlation Coefficients (r) Between d- and l-Amphetamine Levels and Pharmacodynamic Measures During Final Week

Treatment	Pearson <i>r</i>	SKAMP		PERMP	
		Attention	Depotment	Number Attempted	Number Correct
d-amphetamine					
SLI381 30 mg (n=6)	Mean	-0.388	-0.305	0.456	0.466
	95% CI	(-0.758, -0.019)*	(-0.737, 0.127)	(-0.038, 0.951)	(-0.025, 0.957)
SLI381 20 mg (n=9)	Mean	-0.320	-0.358	0.463	0.450
	95% CI	(-0.674, 0.034)	(-0.625, -0.090)*	(0.254, 0.673)*	(0.239, 0.660)*
SLI381 10 mg (n=8)	Mean	-0.231	-0.156	0.453	0.448
	95% CI	(-0.548, 0.085)	(-0.408, 0.097)	(0.186, 0.721)*	(0.175, 0.721)*
Adderall 10 mg (n=9)	Mean	-0.150	-0.074	0.446	0.469
	95% CI	(-0.466, 0.165)	(-0.309, 0.160)	(0.091, 0.801)*	(0.124, 0.814)*
l-amphetamine					
SLI381 30 mg (n=6)	Mean	-0.376	-0.315	0.462	0.473
	95% CI	(-0.755, 0.004)	(-0.730, 0.990)	(-0.028, 0.953)	(-0.014, 0.960)
SLI381 20 mg (n=9)	Mean	-0.347	-0.369	0.426	0.410
	95% CI	(-0.658, -0.037)*	(-0.653, -0.084)*	(0.223, 0.629)*	(0.208, 0.612)*
SLI381 10 mg (n=8)	Mean	-0.210	-0.145	0.457	0.451
	95% CI	(-0.527, 0.108)	(-0.404, 0.114)	(0.199, 0.716)*	(0.186, 0.716)*
Adderall 10 mg (n=9)	Mean	-0.130	-0.067	0.428	0.451
	95% CI	(-0.438, 0.178)	(-0.311, 0.177)	(0.068, 0.788)*	(0.102, 0.801)*

* $p < 0.05$

Source: *Section 14, Table 3.3.1 and 3.3.2*

The mean Pearson correlation coefficients of d- and l-amphetamine levels with the SKAMP scores were all negative, ranging from -0.067 to -0.388. Although there were only a few subjects (n=6 to 9), 4 out of the 16 coefficients reached statistical significance at the 0.05 level (2-sided).

The mean Pearson correlation coefficients of d- and l-amphetamine levels with the PERMP scores were all positive, ranging from 0.410 to 0.473. Although there were only a few subjects (n=6 to 9), 12 out of the 16 coefficients reached statistical significance at the 0.05 level (2-sided).

The findings indicate there was a moderate relationship between plasma drug levels and pharmacodynamic measures for amphetamine.

11.5 Efficacy Conclusions

The mixed-effect ANOVA disclosed highly significant overall treatment effect (averaged across the scores of the 8 sessions observed under the treatment) for all of the efficacy measures ($p < 0.0001$). Pairwise comparisons of active doses vs. placebo on the overall treatment average indicated that for all of the four measures, significant improvements were seen in favor of the SLI381 doses ($p < 0.0001$) and Adderall 10 mg ($p < 0.001$).

ANOVA results showed also significant treatment-by-session effect ($p < 0.0001$) for all efficacy measures. When compared with placebo, SLI381 30 mg dose showed significantly lower average scores ($p < 0.01$) at all of the time points from 1.5 to 12.0 hours post dose for both SKAMP attention and deportment; SLI381 20 mg dose also showed significantly lower average scores ($p < 0.01$) at all of the time points from 1.5 to 12.0 hours post dose for SKAMP attention and deportment, with 2 exceptions (attention at 1.5 hours and deportment at 12.0 hours); SLI381 10 mg dose demonstrated significantly lower average scores ($p < 0.05$) at the time points from 4.5 to 10.5 hours post dose for SKAMP attention and deportment, with 2 exceptions (attention at 9.0 hours and deportment at 10.5 hours); and Adderall® 10 mg dose had significantly lower average scores ($p < 0.05$) at the time points from 1.5 to 7.5 hours post dose for SKAMP attention and from 1.5 to 10.5 hours post dose for SKAMP deportment.

For PERMP, when compared with placebo, SLI381 30 mg dose showed significantly higher average scores ($p < 0.01$) at all of the time points from 1.5 to 12.0 hours post dose for both PERMP number attempted and number correct; SLI381 20 mg dose also showed significantly higher average scores ($p < 0.05$) at all of the time points from 1.5 to 12.0 hours post dose for PERMP number attempted and number correct; SLI381 10 mg dose demonstrated significantly higher average scores ($p < 0.05$) at the time points from 4.5 to 10.5 hours post dose for PERMP number attempted and number correct; and Adderall® 10 mg dose had significantly higher average scores ($p < 0.05$) at the time points from 1.5 to 9.0 hours post dose for PERMP number attempted and from 4.5 to 10.5 hours post dose for PERMP number correct, with 2 exceptions (number attempted at 4.5 hours and number correct at 7.5 hours post dose).

When compared with Adderall® 10 mg, significant differences ($p < 0.05$) in favor of SLI381 were seen in the mean SKAMP attention from 6.0 to 12.0 hours post dose for the SLI381 30 mg, from 9.0 to 12.0 hours post dose for the SLI381 20 mg, and at 12.0 hours for the SLI381 10 mg. For SKAMP deportment, significant differences ($p < 0.05$) in favor of SLI381 30 mg were seen from 4.5 to 12.0 hours post dose. For both PERMP number attempted and number correct, significant differences ($p < 0.05$) favoring of SLI381 were

seen from 4.5 to 12.0 hours post dose for SLI381 30 mg, from 6.0 to 12.0 hours post for SLI381 20 mg, and at 10.5 hours post dose for SLI381 10 mg.

The ITT analysis revealed significant time course effects for all active treatment groups vs. placebo and dose-dependent improvements with SLI381. Placebo treated subjects showed a pattern of deterioration over the course of the 12 hr observation period. This time-related deterioration from initial performance was most notable for the PERMP measures. In contrast, SLI381 30 mg, 20 mg, and 10 mg as well as Adderall® 10 mg showed rapid improvement in efficacy measures by 1.5 hours post dose, both comparing to placebo and initial performance. In comparison to placebo, SLI381 30 mg, 20 mg, and 10 mg showed continued significant efficacy up to 10.5 to 12 hours post dose for efficacy measures; in contrast, Adderall® 10 mg revealed continued efficacy up to 9 hours post dose.

The results from the PP population were similar to and consistent with those observed for the ITT population, an indication of the robustness of the statistical findings.

For d- and l-amphetamine, respectively, the T_{max} (hr) was 6.78 and 6.94; C_{max} (ng/mL) was 48.81 and 14.80; and AUC_{0-24} (ng.hr/mL) was 703.91 and 216.20, following a single dose administration of SLI381 20 mg.

For d-amphetamine, after 1- week daily administration of SLI381 30 mg, 20 mg, or 10 mg, the C_{max} (ng/mL) was 89.04, 54.63, and 28.82, respectively; AUC_{0-24} (ng.hr/mL) was 1364.37, 777.24, and 431.88, respectively; and the T_{max} (hr) was 5.50, 5.83, and 6.38, respectively, compared to about 3.33 hours for Adderall® 10 mg. For l-amphetamine, after one week daily administration of SLI381 30 mg, 20 mg, or 10 mg, the C_{max} (ng/mL) was 28.08, 17.15, and 8.82, respectively; AUC_{0-24} (ng.hr/mL) was 443.53, 261.63, and 138.34, respectively; and the T_{max} (hr) was 5.50, 5.67, and 6.38, respectively, compared to about 3.22 hours for Adderall® 10 mg.

Compared to a single 20 mg dose, the amount of drug accumulation after one week daily administration of SLI381 20 mg was very small as measured by area under the curve.

The study observed a moderate relationship between plasma drug levels and pharmacodynamic measures for amphetamine.

12. SAFETY EVALUATION

12.1 Data Sets Analyzed

Safety information collected from all study participants (n=51) was utilized to assess for drug safety. The information includes AMEs, clinical laboratory tests, vital signs, physical examination, and medical history. Subjects' scores of the Side Effect Rating

Scale rated by parent and teacher were also reported descriptively for each treatment condition.

12.2 Extent of Exposure

Subject drug exposure during the randomized treatment weeks is presented in *Section 14, Table 4.1.1* and summarized in Table 14. All of the 51 study participants received a single SLI381 20 mg dose at the practice visit. During the randomized treatment phase, length of exposure for most subjects was between 4 to 7 days for each treatment.

Table 14 Subject Drug Exposure During Randomized Phases (N=51)

Length of exposure (days)	Treatment				
	SLI381 10 mg	SLI381 20 mg	SLI381 30 mg	Placebo	Adderall® 10 mg
0	3	1	2	2	3
1	0	1	0	0	0
2-3	0	0	0	1	0
4-7	39	40	41	38	37
8-14	9	9	8	10	11

Source: *Section 14, Table 4.1.1*

12.3 Adverse Medical Experiences (AMEs)

12.3.1 Brief Summary of Adverse Medical Experiences

Section 14, Tables 5.1.1 and 5.1.3 present the number of AMEs by body system and preferred term. Listings of the individual adverse medical experiences are contained in *Section 16, Appendix VII, Tables 18.1 through 18.3*. Table 15 summarizes the number of subjects reporting AMEs by body system and preferred term ($\geq 10\%$ of any treatment). Table 16 summarizes the number of post randomization AMEs (≥ 10 AMEs in any treatment).

The overall incidence of subjects reporting any AMEs post randomization was similar between the 5 treatments (ranging between 81.6% for placebo and 93.8% for Adderall® 10 mg). No subjects reported serious AMEs, and no subjects died during the study. Two subjects discontinued due to an AME: 1 subject while receiving placebo and 1 subject while receiving SLI381 20 mg.

12.3.2 Number and Percent of Subjects Reporting Adverse Medical Experiences

Section 14, Tables 5.2.1, 5.2.2, 5.2.3, 5.2.4, and 5.2.5 present the number and percent of patients reporting AMEs post randomization. During the double-blind treatment weeks, subjects reported a total of 919 AMEs (Table 16). The overall incidence of any AMEs was similar among treatments: 40 subjects (81.6%) reported 161 AMEs while receiving placebo, 45 subjects (93.8%) reported 200 AMEs while receiving Adderall® 10 mg, 40 subjects (83.3%) reported 174 AMEs while receiving SLI381 10 mg, 45 subjects (90.0%)

reported 200 AMEs while receiving SLI381 20 mg, and 41 subjects (83.7%) reported 184 AMEs while receiving SLI381 30 mg. Thirty-six subjects (73.5%) reported AMEs that were classified as possibly treatment-related while receiving placebo, 41 subjects (85.4%) while receiving Adderall® 10 mg, 35 subjects (72.9%) while receiving SLI381 10 mg, 39 subjects (78.0%) while receiving SLI381 20 mg, and 39 subjects (79.6%) while receiving SLI381 30 mg. No AMEs were considered definitely treatment-related.

The most commonly reported AMEs were nervousness, anorexia, abdominal pain, insomnia, and headache.

The number of patients reporting AMEs classified as severe in intensity was similar across the treatments (*Section 14, Table 5.2.6*): 7 (14.3%) while taking placebo, 8 (16.7%) while taking Adderall® 10 mg, 6 (12.5%) while taking SLI381 10 mg, 9 (18.0%) while taking SLI381 20 mg, and 8 (16.3%) while taking SLI381 30 mg. The most frequent AMEs classified as severe in intensity were nervousness, insomnia, anorexia, and headache.

Table 15 Number (%) of Subjects Reporting Post Randomization Adverse Medical Experiences (≥ 10% of any Treatment)

(COSTART) Body System Preferred Term	Number (%) of Subjects*				
	SLI381 10 mg	SLI381 20 mg	SLI381 30 mg	Placebo	Adderall® 10 mg
Subjects with any AMEs	40 (83.3)	45 (90.0)	41 (83.7)	40 (81.6)	45 (93.8)
Body as a Whole					
Abdominal pain	14 (29.2)	18 (36.0)	17 (34.7)	12 (24.5)	16 (33.3)
Headache	12 (25.0)	15 (30.0)	12 (24.5)	12 (24.5)	12 (25.0)
Asthenia	8 (16.7)	12 (24.0)	11 (22.4)	8 (16.3)	11 (22.9)
Malaise	7 (14.6)	8 (16.0)	4 (8.2)	7 (14.3)	11 (22.9)
Digestive					
Anorexia	13 (27.1)	20 (40.0)	27 (55.1)	11 (22.4)	22 (45.8)
Nervous					
Nervousness	26 (54.2)	28 (56.0)	21 (42.9)	29 (59.2)	22 (45.8)
Insomnia	6 (12.5)	16 (32.0)	14 (28.6)	10 (20.4)	17 (35.4)
Anxiety	13 (27.1)	11 (22.0)	9 (18.4)	10 (20.4)	11 (22.9)
Emotional lability	13 (27.1)	9 (18.0)	6 (12.2)	5 (10.2)	10 (20.8)
Depression	5 (10.4)	11 (22.0)	3 (6.1)	5 (10.2)	4 (8.3)
Personality disorder	5 (10.4)	1 (2.0)	2 (4.1)	5 (10.2)	6 (12.5)

* Subjects reporting more than one episode under each preferred term were counted only once.

Source: *Section 14, Table 5.2.2*

Table 16 Number of Post Randomization Adverse Medical Experiences Reported (≥ 10 Episodes in any Treatment)

(COSTART) Body system Preferred term	Number of AMEs				
	SLI381 10 mg	SLI381 20 mg	SLI381 30 mg	Placebo	Adderall® 10 mg
Total Events	174	200	184	161	200
Body as a Whole					
Abdominal pain	14	19	19	14	21
Headache	14	18	15	14	17
Asthenia	9	14	12	10	15
Malaise	7	10	4	8	13
Digestive					
Anorexia	13	24	36	11	27
Nervous					
Nervousness	44	35	28	39	33
Insomnia	8	17	18	10	18
Anxiety	15	11	9	12	12
Emotional lability	18	13	9	6	10

Source: Section 14, Table 5.1.1

12.4 Deaths, Other Serious Adverse Events, Subjects Withdrawn for AMEs, and Other Significant Adverse Events

12.4.1 Deaths

No deaths were reported during the study.

12.4.2 Other Serious Adverse Medical Experiences

No serious AMEs were reported during the study (Section 14, Table 5.3.1).

12.4.3 Other Significant Adverse Medical Experiences

No other significant AMEs were reported during the study.

12.4.4 Subjects Withdrawn for Adverse Medical Experiences

Two of 51 (3.9%) subjects withdrew from the study due to AMEs (Section 14, Table 5.3.2). One subject (#3-11) withdrew due to agitation while receiving placebo, and 1 subject (#1-08) withdrew due to stomach ache while receiving SLI381 20 mg. Narratives of these subjects are presented in Section 12.4.5.

12.4.5 Narratives of Subjects Withdrawn for Adverse Medical Experiences

- **Subject 1-08**, a 9-year-old white male diagnosed with ADHD combined subtype, experienced stomach ache while receiving SLI381 20 mg. This event, considered severe in intensity, began on October 23, 1999 (the practice day with a single dose of SLI381 20 mg). The subject had AMEs of insomnia (moderate), appetite loss (severe), picking at skin and clothing (mild), and alternate hot and cold flashes

(moderate) on the same day. He took his first dose of double-blind medication (SLI381 20 mg) on October 24, 1999. Medication was stopped that day, and he was discontinued from the study on November 2, 1999. The subject had a medical history of ongoing enuresis since July 1999 and was not taking any concomitant medications at the time of the events. The investigator considered all events possibly related to study drug. All events resolved on October 24, 1999.

- **Subject 3-11**, a 7-year-old black male diagnosed with ADHD combined subtype, experienced agitation while receiving placebo. This event, considered moderate in intensity, began on November 29, 1999 (Day 38 of double-blind treatment). The subject had previous AMEs of crabby-irritable, buccal-lingual movements, and vomiting (all considered mild in intensity) while taking SLI381 10 mg; appetite loss (mild), crabby-irritable (mild), tearful (mild), sad (mild), depressed (mild), worried (mild), anxious (mild), motor tics (mild), insomnia (severe), and listless (mild) while taking SLI381 20 mg; appetite loss and insomnia (both considered moderate in intensity) while taking SLI381 30 mg; irritable (moderate), depressed (mild), and insomnia (mild) while taking Adderall[®] 10 mg; and irritable (moderate) and depressed (mild) while taking placebo. The subject had no remarkable medical history and was not taking concomitant medications during the study. He was discontinued from the study on Day 39. The investigator considered all AMEs possibly related to study drug. All events resolved within 1 day of onset.

12.5 Clinical Laboratory Results

Section 14, Table 8.1.1 provides summaries of laboratory findings, and *Section 14, Table 8.2.1* has a listing of all subjects with abnormal laboratory results at the end of the study.

12.5.1 Hematology

Most subjects had normal hematology values at end of study. There were abnormal hematology values that occurred infrequently. The following abnormal values occurred in 5 or more subjects: high eosinophils (16 subjects); high neutrophils, segments (7 subjects); high lymphocytes (6 subjects); and low hematocrit (6 subjects). These abnormal values could not be attributed to a specific treatment since they were observed at the end of the crossover study after subjects had received multiple treatments. *Section 16, Appendix VII, Table 19.3* has listings of individual subjects' hematology values.

12.5.2 Chemistry

Most subjects had normal chemistry values at end of study. Abnormal chemistry values occurred infrequently. Six subjects had high abnormal glucose values at end of study. These abnormal values could not be attributed to a specific treatment since they were observed at the end of the crossover study after subjects had received multiple treatments. *Section 16, Appendix VII, Table 19.2* has listings of individual subjects' chemistry values.

12.5.3 Urinalysis

Most subjects had normal urinalyses at end of study. Abnormal urinalyses occurred infrequently. The following were present in 5 or more subjects: bacteria (17 subjects) and mucous threads (11 subjects). These abnormal values could not be attributed to a specific treatment since they were observed at the end of the crossover study after subjects had received multiple treatments. *Section 16, Appendix VII, Table 19.4* has listings of individual subjects' urinalysis values.

12.6 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.6.1 Vital Signs

Descriptive statistics for sitting systolic blood pressure, sitting diastolic blood pressure, and sitting pulse rate are included in *Section 14, Tables 6.1.1, 6.1.2, and 6.1.3* respectively. *Section 16, Appendix VII, Table 16.1* has listings of individual subjects' vital signs. Mean vital signs readings were similar across treatments (including placebo) and from time point to time point (measured at pre dose and at 1.5, 4.5, and 7.5 hours post dose). Minimum and maximum readings were also similar across treatments and time points. Unusually high or low readings were sporadic and infrequent, and no trends were noted.

12.6.2 Physical Examinations

Four subjects had clinically significant physical examination changes from screening to follow-up (*Section 14, Tables 9.1.1 and 9.1.2*). One 12-year-old female subject had mild facial acne, 1 male subject had a small posterior cervical node, and 2 male subjects had mild cervical adenopathy secondary to URI. These abnormalities could not be attributed to a specific treatment since they were observed at the end of the crossover study after subjects had received multiple treatments. *Section 16, Appendix VII, Table 17.1* has listings of individual subjects' physical examination results.

12.6.3 Medical History

Forty-four subjects (86%) had some type of medical abnormality at screening. The most common abnormalities were in the respiratory (9 subjects), CNS and sense organs (10 subjects), and other (15 subjects) body systems as described in *Section 14, Table 10.1.1*. The most common ongoing medical abnormalities were allergies. Ongoing medical abnormalities are listed in *Section 14, Table 10.1.2*.

12.6.4 Other Safety Measures

Mean values for the Side Effect Rating Scale were similar across treatments. Results from the parent version of the scale showed the lowest mean score (fewer and/or less severe side effects) at the SLI381 10 mg dose, while results from the teacher version of the scale showed the lowest mean score at the SLI381 30 mg dose. *Section 14, Table*

7.1.1 presents mean values for the Side Effect Rating Scale; Section 16, Appendix VII, Table 15.1 has individual subjects' Side Effect Rating Scale scores.

12.7 Safety Conclusions

Overall, SLI381 appears to be safe and well-tolerated. A total of 919 AMEs were reported post randomization. Most of the AMEs were mild or moderate in intensity. None of the AMEs were considered definitely treatment-related. The incidence of subjects reporting AMEs was similar across the 5 treatments, with no evidence of a dose-response relationship among the SLI381 doses. No unusual or serious AMEs were reported in this study. The most commonly reported AMEs were nervousness, anorexia, abdominal pain, insomnia, and headache, all of which are typical side effects of amphetamines.

Two subjects (3.9%) discontinued due to AMEs: 1 subject while receiving placebo and 1 subject while receiving SLI381 20 mg. There were no deaths during the study.

Mean values for clinical laboratory tests, vital signs, physical examinations, and the Side Effect Rating Scale were similar across treatments including placebo. Most abnormal hematology, chemistry, and urinalysis results were infrequent and sporadic.

13. DISCUSSION AND OVERALL CONCLUSIONS

The objective of this study was to evaluate the efficacy and safety of 3 doses of SLI381 compared with placebo and with Adderall® 10 mg, to assess the time course of the therapeutic response to SLI381, and to examine the pharmacokinetic profile of SLI381 after single dose and at steady state.

Efficacy

The mixed-effect ANOVA disclosed highly significant overall treatment effect (averaged across the scores of the 8 sessions observed under the treatment) for all of the efficacy measures. Pairwise comparisons of active doses vs. placebo on the overall treatment average indicated that for all of the four measures, significant improvements were seen in favor of the SLI381 doses and Adderall 10 mg.

When compared with placebo, subjects on SLI381 30 mg and 20 mg showed highly significant improvements from 1.5 to 12.0 hours post dose for both SKAMP attention and deportment, and subjects on SLI381 10 mg demonstrated significant improvements from 4.5 to 10.5 hours post dose for SKAMP attention and deportment. In contrast, Adderall® 10 mg had significant improvements from 1.5 to 7.5 hours post dose for SKAMP attention and from 1.5 to 10.5 hours post dose for SKAMP deportment.

For PERMP, when compared with placebo, subjects on SLI381 30 mg and 20 mg showed highly significant improvement from 1.5 to 12.0 hours post dose for both PERMP

number attempted and number correct, and subjects on SLI381 10 mg demonstrated significant improvement from 4.5 to 10.5 hours post dose for PERMP number attempted and number correct. In contrast, Adderall® 10 mg had significant improvement from 1.5 to 9.0 hours post dose for PERMP number attempted and from 4.5 to 10.5 hours post dose for PERMP number correct.

When compared with Adderall® 10 mg, significant improvements on the efficacy measures were seen from 4.5 to 12.0 hours post dose in favor of the SLI381 30 mg, from 6.0 to 12.0 hours post dose in favor of the SLI381 20 mg, and from 10.5 to 12.0 hours in favor of the SLI381 10 mg.

The ITT analysis revealed significant time course effects for all active treatment groups vs. placebo and dose-dependent improvements with SLI381. Placebo-treated subjects showed a pattern of deterioration over the course of the 12-hour observation period. This time-related deterioration from initial performance (i.e., the first classroom session) was most notable for the PERMP measures. In contrast, SLI381 30 mg, 20 mg, and 10 mg as well as Adderall® 10 mg showed rapid improvement in efficacy measures by 1.5 hours post dose, both compared to placebo and initial performance. In comparison to placebo, SLI381 30 mg, 20 mg, and 10 mg showed continued significant efficacy up to 10.5 to 12 hours post dose for efficacy measures; in contrast, Adderall® 10 mg revealed efficacy up to 9 hours post dose.

The results from the PP population were similar to and consistent with those observed for the ITT population, an indication of the robustness of the statistical findings.

Pharmacokinetics

For d- and l-amphetamine, respectively, the T_{max} (hr) was 6.78 and 6.94; C_{max} (ng/mL) was 48.81 and 14.80; and AUC_{0-24} (ng.hr/mL) was 703.91 and 216.20, following a single dose administration of SLI381 20 mg.

For d-amphetamine, after 1-week daily administration of SLI381 30 mg, 20 mg, or 10 mg, the C_{max} (ng/mL) was 89.04, 54.63, and 28.82, respectively; AUC_{0-24} (ng.hr/mL) was 1364.37, 777.24, and 431.88, respectively; and the T_{max} (hr) was 5.50, 5.83, and 6.38, respectively, compared to about 3.33 hours for Adderall® 10 mg. For l-amphetamine, after one week daily administration of SLI381 30 mg, 20 mg, or 10 mg, the C_{max} (ng/mL) was 28.08, 17.15, and 8.82, respectively; AUC_{0-24} (ng.hr/mL) was 443.53, 261.63, and 138.34, respectively; and the T_{max} (hr) was 5.50, 5.67, and 6.38, respectively, compared to about 3.22 hours for Adderall® 10 mg.

Compared to a single 20 mg dose, the amount of drug accumulation after one week daily administration of SLI381 20 mg was very small as measured by area under the curve. After one week daily administration, the T_{max} of SLI381 10 mg was about 6.4 hours for

both d- and l-amphetamine, which was approximately twice as long as that of Adderall® 10 mg.

PK/PD relationship

The study observed a moderate relationship between plasma drug levels and pharmacodynamic measures for amphetamine.

Safety

Overall, SLI381 appears to be safe and well-tolerated. A total of 919 AMEs was reported post randomization. Most of the AMEs was mild or moderate in intensity. None of the AMEs was considered definitely treatment-related. The incidence of subjects reporting AMEs was similar across the 5 treatments. No unusual or serious AMEs were reported in this study. The most commonly reported AMEs were nervousness, anorexia, abdominal pain, insomnia, and headache, all of which are typical side effects of amphetamines.

Two subjects (3.9%) discontinued due to AMEs: 1 subject while receiving placebo and 1 subject while receiving SLI381 20 mg. There were no deaths during the study.

Mean values for clinical laboratory tests, vital signs, physical examinations, and the Side Effect Rating Scale were similar across treatments. Abnormal chemistry, hematology, and urinalysis results were sporadic and infrequent.

Overall conclusions

SLI381 appears to be an efficacious treatment for childhood ADHD. Depending upon doses, rapid onset occurred within the hour of dosing with amphetamine. The persistence of effect of SLI381 doses lasted throughout the day and into early evening, for a duration of about 10 to 12 hours, suggesting that this medication provides a longer duration of action. Maintenance of amphetamine concentrations is sufficient to extend the duration of action of the drug. There appears to be a clear dose-response relationship with SLI381 in terms of efficacy. SLI381 doses appear to be safe and well-tolerated.

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Table 1A	Location of Source Data Used in Tables and Figures	74
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LIST OF TABLES

Table 1.1.1	Demographic and Enrollment Information by Site- Study Participants.....	81
Table 1.1.2	Demographic Characteristics by Site- Study Participants.....	84
Table 1.1.3	Disease Diagnosis and Treatment-Related Characteristics by Site- Study Participants.....	85
Table 1.1.4	Demographic Characteristics by Treatment Sequence - Study Participants.....	86
Table 1.1.5	Disease Diagnosis and Treatment-Related Characteristics by Treatment Sequence - Study Participants.....	87
Table 1.2.1	Randomization and Study Outcome of Individual Subjects by Site	88
Table 1.2.2	Summary of Subject Randomization by Site	91
Table 1.2.3	Summary of Subject Study Outcome by Site.....	92
Table 1.2.4	Summary of Subject Study Outcome by Treatment.....	93
Table 1.2.5	Listing of Early Terminations by Site	94
Table 1.3.1	Subject Treatment Compliance During the Core Treatment Weeks- Randomized Subjects	95
Table 2.1.1	Study-Defined Analysis Populations by Site	96
Table 2.1.2	Demographic Characteristics of the Study-Defined Analysis Populations	97
Table 2.1.3	Disease Diagnosis and Treatment Characteristics of the Study- Defined Analysis Populations	98
Table 2.2.1	Descriptive Statistics of SKAMP Scores Obtained After Administration of a Single SLI381 20 mg Dose	99
Table 2.2.2	Descriptive Statistics of PERMP Scores Obtained After Administration of a Single SLI381 20 mg Dose	102
Table 2.3.1	Descriptive Statistics of SKAMP Attention Scores Obtained During Randomized Treatment for the ITT Population.....	105
Table 2.3.2	Descriptive Statistics of SKAMP Department Scores Obtained During the Core Treatment Weeks for the ITT Population.....	106
Table 2.3.3	Mixed-Model ANOVA of SKAMP Attention Scores for the ITT Population.....	107
Table 2.3.4	Planned Pairwise Mean Comparisons of SKAMP Attention Scores between Active and Reference Drug for the ITT Population.....	108
Table 2.3.5	Mixed-Model ANOVA of SKAMP Department Scores for the ITT Population.....	109
Table 2.3.6	Planned Pairwise Mean Comparisons of the SKAMP Department Scores between Active and Reference Drug for the ITT Population	110

Final

Date: July 31, 2000

10-6022

Table 2.3.7	Descriptive Statistics of PERMP Number Attempted Obtained During Core Treatment Weeks for the ITT Population.....	111
Table 2.3.8	Descriptive Statistics of PERMP Number Correct Obtained During Core Treatment Weeks for the ITT Population.....	112
Table 2.3.9	Mixed-Model ANOVA of PERMP Number Attempted for the ITT Population.....	113
Table 2.3.10	Planned Pairwise Mean Comparisons of PERMP Number Attempted between Active and Reference Drug for the ITT Population.....	114
Table 2.3.11	Mixed-Model ANOVA of PERMP Number Correct for the ITT Population.....	115
Table 2.3.12	Planned Pairwise Mean Comparisons of PERMP Number Correct between Active and Reference Drug for the ITT Population.....	116
Table 2.4.1	Descriptive Statistics of SKAMP Attention Scores Obtained During Core Treatment Weeks for the PP Population.....	117
Table 2.4.2	Descriptive Statistics of SKAMP Department Scores Obtained During Core Treatment Weeks for the PP Population.....	118
Table 2.4.3	Mixed-Model ANOVA of SKAMP Attention Scores for the PP Population.....	119
Table 2.4.4	Planned Pairwise Mean Comparisons of SKAMP Attention Scores between Active and Reference Drug for the PP Population.....	120
Table 2.4.5	Mixed-Model ANOVA of SKAMP Department Scores for the PP Population.....	121
Table 2.4.6	Planned Pairwise Mean Comparisons of SKAMP Department Scores between Active and Reference Drug for the PP Population.....	122
Table 2.4.7	Descriptive Statistics of PERMP Number Attempted Obtained During Core Treatment Weeks for the PP Population.....	123
Table 2.4.8	Descriptive Statistics of PERMP Number Correct Obtained During Core Treatment Weeks for the PP Population.....	124
Table 2.4.9	Mixed-Model ANOVA of PERMP Number Attempted for the PP Population.....	125
Table 2.4.10	Planned Pairwise Mean Comparisons of PERMP Number Attempted between Active and Reference Drug for the PP Population.....	126
Table 2.4.11	Mixed-Model ANOVA of PERMP Number Correct for the PP Population.....	127
Table 2.4.12	Planned Pairwise Mean Comparisons of PERMP Number Correct between Active and Reference Drug for the PP Population.....	128
Table 2.5.1	Descriptive and Inferential Statistics for the Placebo Adjusted SKAMP Attention Scores Obtained During the Core Treatment Weeks for the PP Population.....	129
Table 2.5.2	Descriptive and Inferential Statistics for the Placebo Adjusted SKAMP Department Scores Obtained During the Core Treatment Weeks for the PP Population.....	130

Table 2.5.3	Descriptive and Inferential Statistics for the Placebo Adjusted PERMP Number Attempted Obtained During the Core Treatment Weeks for the PP Population.....	131
Table 2.5.4	Descriptive and Inferential Statistics for the Placebo Adjusted PERMP Number Correct Obtained During the Core Treatment Week for the PP Population	132
Table 3.1.1	Descriptive Statistics for the Plasma Drug Concentration Observed After a Single Dose Administration of SLI 381 20 mg.....	133
Table 3.1.2	Descriptive Statistics for the Plasma PK Parameters Observed After a Single Dose Administration of SLI 381 20 mg	134
Table 3.2.1	Descriptive Statistics for the Plasma D-Amphetamine Concentration Observed at Steady State During the Makeup Week	135
Table 3.2.2	Descriptive Statistics for the Plasma D-Amphetamine PK Parameters Observed at Steady State During the Makeup Week	136
Table 3.2.3	Descriptive Statistics for the Plasma L-Amphetamine Observed at Steady State During the Makeup Week.....	137
Table 3.2.4	Descriptive Statistics for the Plasma L-Amphetamine PK Parameters Observed at Steady State During the Makeup Week	138
Table 3.2.5	Comparative Analysis of the Steady State PK Parameters	139
Table 3.2.6	Comparative Analysis of the Steady State Plasma Drug Levels between SLI381 10 mg and Adderall® 10 mg by Sampling Time.....	140
Table 3.3.1	Descriptive Statistics of the Pearson Correlation Coefficients (r) Between the D-Amphetamine Levels and the PD Measures Obtained During the Makeup Week	141
Table 3.3.2	Descriptive Statistics of the Pearson Correlation Coefficients (r) Between the L-Amphetamine Levels and the PD Measures Obtained During the Makeup Week	142
Table 4.1.1	Patient Drug Exposure During Randomized Treatment Weeks.....	143
Table 5.1.1	Number of Adverse Medical Experiences by Body System and Preferred Term.....	144
Table 5.1.2	Number of Adverse Medical Experiences by Body System and Preferred Term – Serious Events.....	147
Table 5.1.3	Number of Adverse Medical Experiences by Body System and Preferred Term – Non-serious Events	148
Table 5.2.1	Number (%) of Patients Reporting Post-Randomization Adverse Medical Experiences by Body System and Preferred Term – All Causality	151
Table 5.2.2	Number (%) of Patients Reporting Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term.....	157

Table 5.2.3	Number (%) of Patients Reporting Unrelated Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term.....	159
Table 5.2.4	Number (%) of Patients Reporting Possibly Related Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term	161
Table 5.2.5	Number (%) of Patients Reporting Related Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term.....	163
Table 5.2.6	Number (%) of Patients Reporting Related or Possibly Related Severe Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term.....	164
Table 5.3.1	List of Serious Adverse Events	165
Table 5.3.2	List of Patients Withdrawn Due to Adverse Medical Experiences	166
Table 6.1.1	Descriptive Statistics for the Sitting Systolic Blood Pressure (mm Hg).....	167
Table 6.1.2	Descriptive Statistics for the Sitting Diastolic Blood Pressure (mm Hg).....	168
Table 6.1.3	Descriptive Statistics for the Sitting Pulse Rate (bpm)	169
Table 7.1.1	Descriptive Statistics for the Side Effect Rating Scale Obtained During the Core Randomization Treatment Weeks (Visits 3-7).....	170
Table 8.1.1	Descriptive Statistics for the Laboratory Parameters	171
Table 8.2.1	Listing of the End of Study Abnormal Laboratory Parameters.....	175
Table 9.1.1	Number (%) of Patients with Clinically Significant Physical Examination Changes from Screening to Follow-up	181
Table 9.1.2	Listing of Clinically Significant Physical Examination Changes from Screening to Follow-up	182
Table 10.1.1	Number (%) of Patients with Medical Abnormalities at Screening	183
Table 10.1.2	Listing of Ongoing Medical Conditions.....	184
Table 11.1.1	Listing of Concomitant Medications Received During the Study	185

LIST OF FIGURES

Figure 1.1.1	Plasma Drug Concentration-Time Average at Steady State: D-Amphetamine	195
Figure 1.1.2	Plasma Drug Concentration-Time Average at Steady State: L-Amphetamine.....	196
Figure 1.1.3	Plasma Drug Concentration-Time Average Following A Single Dose of SLI381 20 mg	197
Figure 2.1.1	Mean SKAMP Scores and Plasma Drug Concentration Averages: Make-Up Week	198

Figure 2.1.2 Mean PERMP Scores and Plasma Concentration Averages:
Make-Up Week 199

14. TABLES, FIGURES, AND GRAPHS REFERRED TO BUT NOT INCLUDED IN THE TEXT

Table 1A	Location of Source Data Used in Tables and Figures	73
----------	--	----

LIST OF TABLES

Table 1.1.1	Demographic and Enrollment Information by Site– Study Participants ...	80
Table 1.1.2	Demographic Characteristics by Site- Study Participants.....	83
Table 1.1.3	Disease Diagnosis and Treatment-Related Characteristics by Site– Study Participants.....	84
Table 1.1.4	Demographic Characteristics by Treatment Sequence - Study Participants.....	85
Table 1.1.5	Disease Diagnosis and Treatment-Related Characteristics by Treatment Sequence - Study Participants	86
Table 1.2.1	Randomization and Study Outcome of Individual Subjects by Site	87
Table 1.2.2	Summary of Subject Randomization by Site	90
Table 1.2.3	Summary of Subject Study Outcome by Site.....	91
Table 1.2.4	Summary of Subject Study Outcome by Treatment.....	92
Table 1.2.5	Listing of Early Terminations by Site	93
Table 1.3.1	Subject Treatment Compliance During the Core Treatment Weeks– Randomized Subjects	94
Table 2.1.1	Study-Defined Analysis Populations by Site	95
Table 2.1.2	Demographic Characteristics of the Study-Defined Analysis Populations	96
Table 2.1.3	Disease Diagnosis and Treatment Characteristics of the Study- Defined Analysis Populations	97
Table 2.2.1	Descriptive Statistics of SKAMP Scores Obtained After Administration of a Single SLI381 20 mg Dose	98
Table 2.2.2	Descriptive Statistics of PERMP Scores Obtained After Administration of a Single SLI381 20 mg Dose	101
Table 2.3.1	Descriptive Statistics of SKAMP Attention Scores Obtained During Randomized Treatment for the ITT Population.....	104
Table 2.3.2	Descriptive Statistics of SKAMP Department Scores Obtained During the Core Treatment Weeks for the ITT Population.....	105
Table 2.3.3	Mixed-Model ANOVA of SKAMP Attention Scores for the ITT Population.....	106
Table 2.3.4	Planned Pairwise Mean Comparisons of SKAMP Attention Scores between Active and Reference Drug for the ITT Population.....	107
Table 2.3.5	Mixed-Model ANOVA of SKAMP Department Scores for the ITT Population.....	108
Table 2.3.6	Planned Pairwise Mean Comparisons of the SKAMP Department Scores between Active and Reference Drug for the ITT Population.....	109

Final

Date: July 31, 2000

Table 2.3.7	Descriptive Statistics of PERMP Number Attempted Obtained During Core Treatment Weeks for the ITT Population	110
Table 2.3.8	Descriptive Statistics of PERMP Number Correct Obtained During Core Treatment Weeks for the ITT Population.....	111
Table 2.3.9	Mixed-Model ANOVA of PERMP Number Attempted for the ITT Population.....	112
Table 2.3.10	Planned Pairwise Mean Comparisons of PERMP Number Attempted between Active and Reference Drug for the ITT Population.....	113
Table 2.3.11	Mixed-Model ANOVA of PERMP Number Correct for the ITT Population.....	114
Table 2.3.12	Planned Pairwise Mean Comparisons of PERMP Number Correct between Active and Reference Drug for the ITT Population.....	115
Table 2.4.1	Descriptive Statistics of SKAMP Attention Scores Obtained During Core Treatment Weeks for the PP Population	116
Table 2.4.2	Descriptive Statistics of SKAMP Department Scores Obtained During Core Treatment Weeks for the PP Population	117
Table 2.4.3	Mixed-Model ANOVA of SKAMP Attention Scores for the PP Population	118
Table 2.4.4	Planned Pairwise Mean Comparisons of SKAMP Attention Scores between Active and Reference Drug for the PP Population	119
Table 2.4.5	Mixed-Model ANOVA of SKAMP Department Scores for the PP Population.....	120
Table 2.4.6	Planned Pairwise Mean Comparisons of SKAMP Department Scores between Active and Reference Drug for the PP Population	121
Table 2.4.7	Descriptive Statistics of PERMP Number Attempted Obtained During Core Treatment Weeks for the PP Population	122
Table 2.4.8	Descriptive Statistics of PERMP Number Correct Obtained During Core Treatment Weeks for the PP Population.....	123
Table 2.4.9	Mixed-Model ANOVA of PERMP Number Attempted for the PP Population.....	124
Table 2.4.10	Planned Pairwise Mean Comparisons of PERMP Number Attempted between Active and Reference Drug for the PP Population	125
Table 2.4.11	Mixed-Model ANOVA of PERMP Number Correct for the PP Population.....	126
Table 2.4.12	Planned Pairwise Mean Comparisons of PERMP Number Correct between Active and Reference Drug for the PP Population	127
Table 2.5.1	Descriptive and Inferential Statistics for the Placebo Adjusted SKAMP Attention Scores Obtained During the Core Treatment Weeks for the PP Population.....	128
Table 2.5.2	Descriptive and Inferential Statistics for the Placebo Adjusted SKAMP Department Scores Obtained During the Core Treatment Weeks for the PP Population.....	129

Table 2.5.3	Descriptive and Inferential Statistics for the Placebo Adjusted PERMP Number Attempted Obtained During the Core Treatment Weeks for the PP Population.....	130
Table 2.5.4	Descriptive and Inferential Statistics for the Placebo Adjusted PERMP Number Correct Obtained During the Core Treatment Week for the PP Population.....	131
Table 3.1.1	Descriptive Statistics for the Plasma Drug Concentration Observed After a Single Dose Administration of SLI 381 20 mg.....	132
Table 3.1.2	Descriptive Statistics for the Plasma PK Parameters Observed After a Single Dose Administration of SLI 381 20 mg.....	133
Table 3.2.1	Descriptive Statistics for the Plasma D-Amphetamine Concentration Observed at Steady State During the Makeup Week.....	134
Table 3.2.2	Descriptive Statistics for the Plasma D-Amphetamine PK Parameters Observed at Steady State During the Makeup Week.....	135
Table 3.2.3	Descriptive Statistics for the Plasma L-Amphetamine Observed at Steady State During the Makeup Week.....	136
Table 3.2.4	Descriptive Statistics for the Plasma L-Amphetamine PK Parameters Observed at Steady State During the Makeup Week.....	137
Table 3.2.5	Comparative Analysis of the Steady State PK Parameters.....	138
Table 3.2.6	Comparative Analysis of the Steady State Plasma Drug Levels between SLI381 10 mg and Adderall® 10 mg by Sampling Time.....	139
Table 3.3.1	Descriptive Statistics of the Pearson Correlation Coefficients (r) Between the D-Amphetamine Levels and the PD Measures Obtained During the Makeup Week.....	140
Table 3.3.2	Descriptive Statistics of the Pearson Correlation Coefficients (r) Between the L-Amphetamine Levels and the PD Measures Obtained During the Makeup Week.....	141
Table 4.1.1	Patient Drug Exposure During Randomized Treatment Weeks.....	142
Table 5.1.1	Number of Adverse Medical Experiences by Body System and Preferred Term.....	143
Table 5.1.2	Number of Adverse Medical Experiences by Body System and Preferred Term – Serious Events.....	146
Table 5.1.3	Number of Adverse Medical Experiences by Body System and Preferred Term – Non-serious Events.....	147
Table 5.2.1	Number (%) of Patients Reporting Post-Randomization Adverse Medical Experiences by Body System and Preferred Term – All Causality.....	150
Table 5.2.2	Number (%) of Patients Reporting Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term.....	156
Table 5.2.3	Number (%) of Patients Reporting Unrelated Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term.....	158

Table 5.2.4	Number (%) of Patients Reporting Possibly Related Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term	160
Table 5.2.5	Number (%) of Patients Reporting Related Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term.....	162
Table 5.2.6	Number (%) of Patients Reporting Related or Possibly Related Severe Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term.....	163
Table 5.3.1	List of Serious Adverse Events	164
Table 5.3.2	List of Patients Withdrawn Due to Adverse Medical Experiences	165
Table 6.1.1	Descriptive Statistics for the Sitting Systolic Blood Pressure (mm Hg).....	166
Table 6.1.2	Descriptive Statistics for the Sitting Diastolic Blood Pressure (mm Hg).....	167
Table 6.1.3	Descriptive Statistics for the Sitting Pulse Rate (bpm)	168
Table 7.1.1	Descriptive Statistics for the Side Effect Rating Scale Obtained During the Core Randomization Treatment Weeks (Visits 3-7).....	169
Table 8.1.1	Descriptive Statistics for the Laboratory Parameters	170
Table 8.2.1	Listing of the End of Study Abnormal Laboratory Parameters.....	174
Table 9.1.1	Number (%) of Patients with Clinically Significant Physical Examination Changes from Screening to Follow-up	180
Table 9.1.2	Listing of Clinically Significant Physical Examination Changes from Screening to Follow-up	181
Table 10.1.1	Number (%) of Patients with Medical Abnormalities at Screening.....	182
Table 10.1.2	Listing of Ongoing Medical Conditions.....	183
Table 11.1.1	Listing of Concomitant Medications Received During the Study	184

LIST OF FIGURES

Figure 1.1.1	Plasma Drug Concentration-Time Average at Steady State: D-Amphetamine	194
Figure 1.1.2	Plasma Drug Concentration-Time Average at Steady State: L-Amphetamine.....	195
Figure 1.1.3	Plasma Drug Concentration-Time Average Following A Single Dose of SLI381 20 mg	196
Figure 2.1.1	Mean SKAMP Scores and Plasma Drug Concentration Averages: Make-Up Week	197
Figure 2.1.2	Mean PERMP Scores and Plasma Concentration Averages: Make-Up Week	198

Table 1A: Location of Source Data Used in Tables and Figures

TABLE NO.	TITLE	SOURCE TABLE*
1.1.1	Demographic and Enrollment Information by Site– Study Participants	3.1 21.1
1.1.2	Demographic Characteristics by Site- Study Participants	3.1
1.1.3	Disease Diagnosis and Treatment-Related Characteristics by Site– Study Participants	4.1 8.1
1.1.4	Demographic Characteristics by Treatment Sequence - Study Participants	1.1 3.1
1.1.5	Disease Diagnosis and Treatment-Related Characteristics by Treatment Sequence - Study Participants	1.1 4.1 8.1
1.2.1	Randomization and Study Outcome of Individual Subjects by Site	1.1 21.1
1.2.2	Summary of Subject Randomization by Site	1.1
1.2.3	Summary of Subject Study Outcome by Site	21.1
1.2.4	Summary of Subject Study Outcome by Treatment	21.1
1.2.5	Listing of Early Terminations by Site	3.1 4.1 8.1 21.1
1.3.1	Subject Treatment Compliance During the Core Treatment Weeks – Randomized Subjects	12.2
2.1.1	Study-Defined Analysis Populations by Site	1.1

TABLE

NO.	TITLE	SOURCE TABLE*
2.1.2	Demographic Characteristics of the Study-Defined Analysis Populations	3.1
2.1.3	Disease Diagnosis and Treatment Characteristics of the Study-Defined Analysis Populations	4.1 8.1
2.2.1	Descriptive Statistics of SKAMP Scores Obtained After Administration of a Single SLI381 20 mg Dose	13.1
2.2.2	Descriptive Statistics of PERMP Scores Obtained After Administration of a Single SLI381 20 mg Dose	14.1
2.3.1	Descriptive Statistics of SKAMP Attention Scores Obtained During Randomized Treatment for the ITT Population	13.1
2.3.2	Descriptive Statistics of SKAMP Department Scores Obtained During the Core Treatment Weeks for the ITT Population	13.1
2.3.3	Mixed-Model ANOVA of SKAMP Attention Scores for the ITT Population	13.1
2.3.4	Planned Pairwise Mean Comparisons of SKAMP Attention Scores between Active and Reference Drug for the ITT Population	13.1
2.3.5	Mixed-Model ANOVA of SKAMP Department Scores for the ITT Population	13.1
2.3.6	Planned Pairwise Mean Comparisons of the SKAMP Department Scores between Active and Reference Drug for the ITT Population	13.1
2.3.7	Descriptive Statistics of PERMP Number Attempted Obtained During Core Treatment Weeks for the ITT Population	14.1
2.3.8	Descriptive Statistics of PERMP Number Correct Obtained During Core Treatment Weeks for the ITT Population	14.1
2.3.9	Mixed-Model ANOVA of PERMP Number Attempted for the ITT Population	14.1
2.3.10	Planned Pairwise Mean Comparisons of PERMP Number Attempted between Active and Reference Drug for the ITT Population	14.1
2.3.11	Mixed-Model ANOVA of PERMP Number Correct for the ITT Population	14.1

Final

Date: July 31, 2000

TABLE NO.	TITLE	SOURCE TABLE*
2.3.12	Planned Pairwise Mean Comparisons of PERMP Number Correct between Active and Reference Drug for the ITT Population	14.1
2.4.1	Descriptive Statistics of SKAMP Attention Scores Obtained During Core Treatment Weeks for the PP Population	13.1
2.4.2	Descriptive Statistics of SKAMP Department Scores Obtained During Core Treatment Weeks for the PP Population	13.1
2.4.3	Mixed-Model ANOVA of SKAMP Attention Scores for the PP Population	13.1
2.4.4	Planned Pairwise Mean Comparisons of SKAMP Attention Scores between Active and Reference Drug for the PP Population	13.1
2.4.5	Mixed-Model ANOVA of SKAMP Department Scores for the PP Population	13.1
2.4.6	Planned Pairwise Mean Comparisons of SKAMP Department Scores between Active and Reference Drug for the PP Population	13.1
2.4.7	Descriptive Statistics of PERMP Number Attempted Obtained During Core Treatment Weeks for the PP Population	14.1
2.4.8	Descriptive Statistics of PERMP Number Correct Obtained During Core Treatment Weeks for the PP Population	14.1
2.4.9	Mixed-Model ANOVA of PERMP Number Attempted for the PP Population	14.1
2.4.10	Planned Pairwise Mean Comparisons of PERMP Number Attempted between Active and Reference Drug for the PP Population	14.1
2.4.11	Mixed-Model ANOVA of PERMP Number Correct for the PP Population	14.1
2.4.12	Planned Pairwise Mean Comparisons of PERMP Number Correct between Active and Reference Drug for the PP Population	14.1

TABLE NO.	TITLE	SOURCE TABLE*
2.5.1	Descriptive and Inferential Statistics for the Placebo Adjusted SKAMP Attention Scores Obtained During the Core Treatment Weeks for the PP Population	13.1
2.5.2	Descriptive and Inferential Statistics for the Placebo Adjusted SKAMP Depoement Scores Obtained During the Core Treatment Weeks for the PP Population	13.1
2.5.3	Descriptive and Inferential Statistics for the Placebo Adjusted PERMP Number Attempted Obtained During the Core Treatment Weeks for the PP Population	14.1
2.5.4	Descriptive and Inferential Statistics for the Placebo Adjusted PERMP Number Correct Obtained During the Core Treatment Week for the PP Population	14.1
3.1.1	Descriptive Statistics for the Plasma Drug Concentration Observed After a Single Dose Administration of SLI 381 20 mg	20.2 20.4
3.1.2	Descriptive Statistics for the Plasma PK Parameters Observed After a Single Dose Administration of SLI 381 20 mg	20.3 20.5
3.2.1	Descriptive Statistics for the Plasma D-Amphetamine Concentration Observed at Steady State During the Makeup Week	20.2
3.2.2	Descriptive Statistics for the Plasma D-Amphetamine PK Parameters Observed at Steady State During the Makeup Week	20.3
3.2.3	Descriptive Statistics for the Plasma L-Amphetamine Observed at Steady State During the Makeup Week	20.4
3.2.4	Descriptive Statistics for the Plasma L-Amphetamine PK Parameters Observed at Steady State During the Makeup Week	20.5
3.2.5	Comparative Analysis of the Steady State PK Parameters	20.3 20.5
3.2.6	Comparative Analysis of the Steady State Plasma Drug Levels between SLI381 10 mg and Adderall® 10 mg by Sampling Time	20.2 20.4

TABLE NO.	TITLE	SOURCE TABLE*
3.3.1	Descriptive Statistics of the Pearson Correlation Coefficients (r) Between the D-Amphetamine Levels and the PD Measures Obtained During the Makeup Week	13.1 14.1 20.2
3.3.2	Descriptive Statistics of the Pearson Correlation Coefficients (r) Between the L-Amphetamine Levels and the PD Measures Obtained During the Makeup Week	13.1 14.1 20.4
4.1.1	Patient Drug Exposure During Randomized Treatment Weeks	12.2
5.1.1	Number of Adverse Medical Experiences by Body System and Preferred Term	18.1 18.2 18.3
5.1.2	Number of Adverse Medical Experiences by Body System and Preferred Term – Serious Events	18.1 18.2 18.3
5.1.3	Number of Adverse Medical Experiences by Body System and Preferred Term – Non-serious Events	18.1 18.2 18.3
5.2.1	Number (%) of Patients Reporting Post-Randomization Adverse Medical Experiences by Body System and Preferred Term – All Causality	18.1 18.2 18.3
5.2.2	Number (%) of Patients Reporting Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term	18.1 18.2 18.3

TABLE NO.	TITLE	SOURCE TABLE*
5.2.3	Number (%) of Patients Reporting Unrelated Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term	18.1 18.2 18.3
5.2.4	Number (%) of Patients Reporting Possibly Related Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term	18.1 18.2 18.3
5.2.5	Number (%) of Patients Reporting Related Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term	18.1 18.2 18.3
5.2.6	Number (%) of Patients Reporting Related or Possibly Related Severe Post-Randomization Adverse Medical Experiences by Treatment Group, Body System, and Preferred Term	18.1 18.2 18.3
5.3.1	List of Serious Adverse Events	18.1 18.2 18.3
5.3.2	List of Patients Withdrawn Due to Adverse Medical Experiences	3.1 21.1
6.1.1	Descriptive Statistics for the Sitting Systolic Blood Pressure (mm Hg)	16.1
6.1.2	Descriptive Statistics for the Sitting Diastolic Blood Pressure (mm Hg)	16.1
6.1.3	Descriptive Statistics for the Sitting Pulse Rate (bpm)	16.1
7.1.1	Descriptive Statistics for the Side Effect Rating Scale Obtained During the Core Randomization Treatment Weeks (Visits 3-7)	15.1

TABLE		
NO.	TITLE	SOURCE TABLE*
8.1.1	Descriptive Statistics for the Laboratory Parameters	19.2 19.3 19.4
8.2.1	Listing of the End of Study Abnormal Laboratory Parameters	19.2 19.3 19.4
9.1.1	Number (%) of Patients with Clinically Significant Physical Examination Changes from Screening to Follow-up	17.1
9.1.2	Listing of Clinically Significant Physical Examination Changes from Screening to Follow-up	17.1
10.1.1	Number (%) of Patients with Medical Abnormalities at Screening	5.1
10.1.2	Listing of Ongoing Medical Conditions	5.1
11.1.1	Listing of Concomitant Medications Received During the Study	4.1
Fig 1	Mean SKAMP Attention Score by Treatment and Classroom Session (ITT)	13.1
Fig 2	Mean SKAMP Deportment Score by Treatment and Classroom Session (ITT)	13.1
Fig 3	Mean PERMP Number Attempted by Treatment and Classroom Session (ITT)	14.1
Fig 4	Mean PERMP Number Correct by Treatment and Classroom Session (ITT)	14.1

* All source tables are located in *Section 16, Appendix VII, Patient Data Listings*.

Table 1.1.1
Demographic and Enrollment Information by Site - Study Participants
Protocol # 381.201

(Page 1 of 3)

Site	Subject Number*	Randomization Number**	Subject Initials	Enrollment Date	End Study Date***	Gender	Race	Age (yr)	Weight (lb)	Height (in)	
Site 1	01	01	████	10/17/1999	12/05/1999	Male	Black	12.0	127.0	60.2	
	03	03	████	10/17/1999	12/14/1999	Male	White	8.0	55.0	51.5	
	04	04	████	10/17/1999	12/05/1999	Female	White	10.0	82.0	57.5	
	05	05	████	10/17/1999	12/05/1999	Male	White	8.0	52.0	51.5	
	07	07	████	10/17/1999	12/05/1999	Male	White	7.0	52.0	51.0	
	08	08	████	10/17/1999	11/02/1999	Male	White	9.0	88.0	54.0	
	09	09	████	10/17/1999	12/05/1999	Male	Black	12.0	110.0	59.5	
	11	11	████	10/17/1999	12/05/1999	Male	White	8.0	62.0	53.5	
	12	12	████	10/17/1999	12/05/1999	Male	White	6.0	52.0	45.5	
	13	13	████	10/17/1999	12/05/1999	Female	White	7.0	53.0	48.5	
	14	14	████	10/17/1999	12/05/1999	Male	White	7.0	68.0	51.3	
	15	06	████	10/17/1999	12/05/1999	Female	Black	9.0	98.0	54.0	
	16	02	████	10/17/1999	12/05/1999	Male	White	7.0	57.0	48.5	
	Site 2	01	01	████	10/03/1999	11/21/1999	Male	Hispanic	11.0	153.0	59.5
		02	02	████	10/03/1999	11/21/1999	Male	Hispanic	8.0	88.0	51.3
		05	03	████	10/03/1999	11/21/1999	Male	Hispanic	11.0	77.0	57.0
06		04	████	10/03/1999	11/21/1999	Male	White	12.0	109.0	58.0	
09		15	████	10/03/1999	11/21/1999	Female	Hispanic	10.0	80.0	58.5	
13		06	████	10/03/1999	11/21/1999	Male	Hispanic	8.0	68.0	51.5	
15		08	████	10/03/1999	11/21/1999	Male	Black	6.0	58.0	49.5	
16		09	████	10/03/1999	11/21/1999	Male	Hispanic	7.0	50.0	47.5	
17		10	████	10/03/1999	11/11/1999	Male	Hispanic	8.0	75.0	48.5	
18		11	████	10/03/1999	11/21/1999	Male	Hispanic	9.0	102.0	55.3	
20	14	████	10/03/1999	11/21/1999	Male	Black	10.0	71.0	55.7		

* Missing subject numbers represent screen failures.

** Missing randomization numbers were not assigned.

*** Last day in study from CRF page 102 (End of Study Form).

Generation: 04MAY00

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Table 1.1.1
Demographic and Enrollment Information by Site - Study Participants
Protocol # 381.201

(Page 2 of 3)

Site	Subject Number*	Randomization Number**	Subject Initials	Enrollment Date	End Study Date***	Gender	Race	Age (yr)	Weight (lb)	Height (in)
Site 2	21	13	█	10/03/1999	11/21/1999	Male	Black	12.0	76.0	59.5
Site 3	02	01	█	10/17/1999	12/05/1999	Male	White	11.0	132.0	61.8
	03	02	█	10/17/1999	12/05/1999	Male	White	9.0	115.0	48.0
	04	03	█	10/17/1999	12/20/1999	Female	White	12.0	146.0	65.2
	06	04	█	10/17/1999	12/05/1999	Male	White	7.0	69.0	51.0
	08	05	█	10/17/1999	12/05/1999	Male	Black	12.0	142.0	58.0
	09	06	█	10/17/1999	11/20/1999	Male	Hispanic	11.0	106.0	59.0
	10	07	█	10/17/1999	11/20/1999	Female	Hispanic	11.0	77.0	58.0
	11	08	█	10/17/1999	12/05/1999	Male	Black	7.0	74.0	49.5
	12	09	█	10/17/1999	12/05/1999	Male	Hispanic	10.0	73.0	54.0
	15	10	█	10/17/1999	12/05/1999	Male	White	11.0	97.0	60.5
	16	11	█	10/17/1999	12/05/1999	Male	Hispanic	8.0	88.0	52.0
	17	12	█	10/17/1999	12/05/1999	Male	Other	8.0	48.0	47.0
	18	13	█	10/17/1999	12/05/1999	Male	Other	7.0	49.0	46.5
	19	14	█	10/17/1999	12/05/1999	Male	White	12.0	103.0	60.3
	20	15	█	10/17/1999	12/05/1999	Male	White	9.0	83.0	55.5
Site 4	01	01	█	09/26/1999	11/14/1999	Female	White	12.0	96.0	62.8
	02	02	█	09/26/1999	11/14/1999	Male	White	9.0	60.0	50.0
	03	03	█	09/26/1999	11/14/1999	Male	White	11.0	68.0	54.0
	04	04	█	09/26/1999	11/14/1999	Male	White	12.0	88.0	57.5
	05	05	█	09/26/1999	11/14/1999	Male	Asian	11.0	161.0	62.0
	06	06	█	09/26/1999	11/14/1999	Male	White	12.0	104.0	63.5
	08	08	█	09/26/1999	11/13/1999	Male	White	11.0	70.0	55.0

* Missing subject numbers represent screen failures.

** Missing randomization numbers were not assigned.

*** Last day in study from CRF page 102 (End of Study Form).

Generation: 04MAY00

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Table 1.1.1
Demographic and Enrollment Information by Site - Study Participants
Protocol # 381.201

(Page 3 of 3)

Site	Subject Number*	Randomization Number**	Subject Initials	Enrollment Date	End Study Date***	Gender	Race	Age (yr)	Weight (lb)	Height (in)
Site 4	09	09	█	09/26/1999	11/14/1999	Male	Asian	11.0	54.0	54.0
	10	10	█	09/26/1999	11/14/1999	Male	Asian	11.0	56.0	55.0
	11	11	█	09/26/1999	11/14/1999	Male	White	11.0	60.0	53.0
	12	12	█	09/26/1999	11/14/1999	Male	Other	9.0	75.0	55.0
Mean							9.5	83.5	54.6	
S.D.							1.9	28.9	4.9	
Minimum				09/26/1999	11/02/1999			6.0	48.0	45.5
Maximum				10/17/1999	12/20/1999			12.0	161.0	65.2

* Missing subject numbers represent screen failures.

** Missing randomization numbers were not assigned.

*** Last day in study from CRF page 102 (End of Study Form).

Generation: 04MAY00

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Table 1.1.2
Demographic Characteristics by Site - Study Participants
Protocol # 381.201

(Page 1 of 1)

Parameter			Total	Site			
				Site 1	Site 2	Site 3	Site 4
Total Subjects	N		51	13	12	15	11
Gender	Male	N (%)	44 (86.3%)	10 (76.9%)	11 (91.7%)	13 (86.7%)	10 (90.9%)
	Female	N (%)	7 (13.7%)	3 (23.1%)	1 (8.3%)	2 (13.3%)	1 (9.1%)
Race	White	N (%)	25 (49.0%)	10 (76.9%)	1 (8.3%)	7 (46.7%)	7 (63.6%)
	Black	N (%)	8 (15.7%)	3 (23.1%)	3 (25.0%)	2 (13.3%)	0 (0.0%)
	Hispanic	N (%)	12 (23.5%)	0 (0.0%)	8 (66.7%)	4 (26.7%)	0 (0.0%)
	Asian	N (%)	3 (5.9%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	3 (27.3%)
	Other	N (%)	3 (5.9%)	0 (0.0%)	0 (0.0%)	2 (13.3%)	1 (9.1%)
Age	6-8 years	N (%)	18 (35.3%)	8 (61.5%)	5 (41.7%)	5 (33.3%)	0 (0.0%)
	9-12 years	N (%)	33 (64.7%)	5 (38.5%)	7 (58.3%)	10 (66.7%)	11 (100.0%)
Age (yr)	N		51	13	12	15	11
	Mean (SD)		9.5 (1.9)	8.5 (1.9)	9.3 (2.0)	9.7 (1.9)	10.9 (1.0)
	Min - Max		6.0 - 12.0	6.0 - 12.0	6.0 - 12.0	7.0 - 12.0	9.0 - 12.0
Weight (lb)	N		51	13	12	15	11
	Mean (SD)		83.5 (28.9)	73.5 (25.3)	83.9 (27.3)	93.5 (30.7)	81.1 (31.2)
	Min - Max		48.0 - 161.0	52.0 - 127.0	50.0 - 153.0	48.0 - 146.0	54.0 - 161.0
Height (in)	N		51	13	12	15	11
	Mean (SD)		54.6 (4.9)	52.8 (4.3)	54.3 (4.4)	55.1 (5.9)	56.5 (4.4)
	Min - Max		45.5 - 65.2	45.5 - 60.2	47.5 - 59.5	46.5 - 65.2	50.0 - 63.5

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Table 1.1.3
Disease Diagnosis and Treatment-Related Characteristics by Site - Study Participants
Protocol # 381.201

(Page 1 of 1)

Parameter			Total	Site			
				Site 1	Site 2	Site 3	Site 4
Total Subjects		N	51	13	12	15	11
Diagnosis	Hyperactive	N (%)	1 (2.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	1 (9.1%)
	Combined	N (%)	50 (98.0%)	13 (100.0%)	12 (100.0%)	15 (100.0%)	10 (90.9%)
Duration Tmt. (yr)		N	47	13	11	12	11
		Mean (SD)	1.7 (1.7)	1.6 (1.8)	2.0 (1.8)	1.6 (1.8)	1.8 (1.5)
		Min - Max	0.0 - 5.7	0.1 - 5.2	0.2 - 5.7	0.1 - 5.0	0.0 - 5.1
Previous Tmt.	None Listed	N (%)	4 (7.8%)	0 (0.0%)	1 (8.3%)	3 (20.0%)	0 (0.0%)
	Amphetamine only	N (%)	17 (33.3%)	5 (38.5%)	4 (33.3%)	4 (26.7%)	4 (36.4%)
	MPH only	N (%)	30 (58.8%)	8 (61.5%)	7 (58.3%)	8 (53.3%)	7 (63.6%)

NOTE: Duration of treatment computed from the medication start and stop dates. Missing day or month of date was replaced by 01 to compute duration.

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Table 1.1.4
Demographic Characteristics by Treatment Sequence - Study Participants
Protocol # 381.201

(Page 1 of 1)

Parameter		Total	Sequence*					
			ABCDE	BCDEA	CDEAB	DEABC	EABCD	
Total Subjects	N	51	12	10	9	11	9	
Gender	Male	N (%)	44 (86.3%)	10 (83.3%)	8 (80.0%)	9 (100.0%)	10 (90.9%)	7 (77.8%)
	Female	N (%)	7 (13.7%)	2 (16.7%)	2 (20.0%)	0 (0.0%)	1 (9.1%)	2 (22.2%)
Race	White	N (%)	25 (49.0%)	6 (50.0%)	6 (60.0%)	2 (22.2%)	6 (54.5%)	5 (55.6%)
	Black	N (%)	8 (15.7%)	0 (0.0%)	2 (20.0%)	4 (44.4%)	1 (9.1%)	1 (11.1%)
	Hispanic	N (%)	12 (23.5%)	4 (33.3%)	1 (10.0%)	1 (11.1%)	3 (27.3%)	3 (33.3%)
	Asian	N (%)	3 (5.9%)	0 (0.0%)	1 (10.0%)	1 (11.1%)	1 (9.1%)	0 (0.0%)
	Other	N (%)	3 (5.9%)	2 (16.7%)	0 (0.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
Age	6-8 years	N (%)	18 (35.3%)	5 (41.7%)	1 (10.0%)	5 (55.6%)	4 (36.4%)	3 (33.3%)
	9-12 years	N (%)	33 (64.7%)	7 (58.3%)	9 (90.0%)	4 (44.4%)	7 (63.6%)	6 (66.7%)
Age (yr)	N	51	12	10	9	11	9	
	Mean (SD)	9.5 (1.9)	8.8 (1.5)	10.6 (1.6)	9.4 (2.2)	9.5 (2.1)	9.7 (2.0)	
	Min - Max	6.0 - 12.0	6.0 - 11.0	7.0 - 12.0	7.0 - 12.0	6.0 - 12.0	7.0 - 12.0	
Weight (lb)	N	51	12	10	9	11	9	
	Mean (SD)	83.5 (28.9)	69.6 (15.7)	99.9 (29.0)	78.7 (30.7)	78.0 (29.4)	95.2 (32.2)	
	Min - Max	48.0 - 161.0	49.0 - 102.0	68.0 - 161.0	48.0 - 142.0	50.0 - 146.0	53.0 - 153.0	
Height (in)	N	51	12	10	9	11	9	
	Mean (SD)	54.6 (4.9)	52.3 (4.1)	57.7 (4.0)	53.8 (4.5)	54.7 (5.4)	55.0 (5.6)	
	Min - Max	45.5 - 65.2	45.5 - 58.0	51.3 - 62.8	47.0 - 59.5	47.5 - 65.2	48.0 - 63.5	

*A=Placebo B=Adderall 10mg C=SLI381 10mg D=SLI381 20mg E=SLI381 30mg

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Table 1.1.5
 Disease Diagnosis and Treatment-Related Characteristics by Treatment Sequence - Study Participants (Page 1 of 1)
 Protocol # 381.201

Parameter		Total	Sequence*					
			ABCDE	BCDEA	CDEAB	DEABC	EABCD	
Total Subjects	N	51	12	10	9	11	9	
Diagnosis	Hyperactive	N (%)	1 (2.0%)	1 (8.3%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
	Combined	N (%)	50 (98.0%)	11 (91.7%)	10 (100.0%)	9 (100.0%)	11 (100.0%)	9 (100.0%)
Dur. Tmt. (yr)	N	47	10	9	8	11	9	
	Mean (SD)	1.7 (1.7)	2.0 (1.5)	2.0 (1.7)	0.7 (1.3)	1.6 (1.4)	2.2 (2.4)	
	Min - Max	0.0 - 5.7	0.1 - 5.0	0.1 - 5.0	0.0 - 4.0	0.0 - 4.6	0.1 - 5.7	
Previous Tmt.	None Listed	N (%)	4 (7.8%)	2 (16.7%)	1 (10.0%)	1 (11.1%)	0 (0.0%)	0 (0.0%)
	Amphetamine only	N (%)	17 (33.3%)	4 (33.3%)	4 (40.0%)	4 (44.4%)	4 (36.4%)	1 (11.1%)
	MPH only	N (%)	30 (58.8%)	6 (50.0%)	5 (50.0%)	4 (44.4%)	7 (63.6%)	8 (88.9%)

*A=Placebo B=Adderall 10mg C=SLI381 10mg D=SLI381 20mg E=SLI381 30mg

NOTE: Duration of treatment computed from the medication start and stop dates. Missing day or month of date was replaced by 01 to compute duration.

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Table 1.2.1
Randomization and Study Outcome of Individual Subjects by Site
Protocol # 381.201

(Page 1 of 3)

Site	Subject Number	Randomization Number	Randomization Date	Treatment Sequence	Study Outcome	Last Visit*	Time on Drug** (days)	
Site 1	01	01	10/23/1999	EABDCD	Complete study	8	42	
	03	03	10/23/1999	DEABCB	Complete study	8	42	
	04	04	10/23/1999	ABCDEB	Complete study	8	42	
	05	05	10/23/1999	ABCDEA	Complete study	8	42	
	07	07	10/23/1999	CDEABE	Complete study	8	42	
	08	08	10/23/1999	DEABCD	AME: STOMACH ACHE	2	1	
	09	09	10/23/1999	CDEABC	Complete study	8	42	
	11	11	10/23/1999	CDEABD	Complete study	8	42	
	12	12	10/23/1999	ABCDEB	Complete study	8	42	
	13	13	10/23/1999	EABCDE	Complete study	8	42	
	14	14	10/23/1999	BCDEAA	Complete study	8	42	
	15	06	10/23/1999	BCDEAA	Complete study	8	42	
	16	02	10/23/1999	DEABCD	Complete study	8	42	
	Site 2	01	01	10/09/1999	EABCDE	Complete study	8	42
		02	02	10/09/1999	CDEABA	Complete study	8	42
		05	03	10/09/1999	DEABCB	Complete study	8	42
06		04	10/09/1999	BCDEAD	Complete study	8	42	
09		15	10/09/1999	EABCDE	Complete study	8	42	
13		06	10/09/1999	ABCDEB	Complete study	8	42	
15		08	10/09/1999	DEABCA	Complete study	8	42	
16		09	10/09/1999	DEABCC	Complete study	8	42	
17		10	10/09/1999	ABCDEE	Other: COULD NOT TOLERATE BEING IN STUDY	4	20	
18		11	10/09/1999	ABCDED	Complete study	8	42	
20		14	10/09/1999	BCDEAB	Complete study	8	42	
21	13	10/09/1999	CDEABD	Complete study	8	42		

* Last study visit with efficacy information.

** Calculated as the date of last dose minus the date of first dose plus one.

NOTE: A=Placebo B=Adderall 10mg C=SLI381 10mg D=SLI381 20mg E=SLI381 30mg

Generation: 04MAY00

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Table 1.2.1
Randomization and Study Outcome of Individual Subjects by Site
Protocol # 381.201

(Page 2 of 3)

Site	Subject Number	Randomization Number	Randomization Date	Treatment Sequence	Study Outcome	Last Visit*	Time on Drug** (days)	
Site 3	02	01	10/23/1999	BCDEAD	Complete study	8	42	
	03	02	10/23/1999	EABCDE	Complete study	8	42	
	04	03	10/23/1999	DEABCE	Other: UCLA IRB EX CRIT: GIRLS WHO HAD MENARCHE	2	14	
	06	04	10/23/1999	EABCDE	Complete study	8	42	
	08	05	10/23/1999	CDEABD	Complete study	8	42	
	09	06	10/23/1999	DEABCB	Lost to follow-up	6	40	
	10	07	10/23/1999	ABCDEC	Lost to follow-up	6	40	
	11	08	10/23/1999	CDEABA	AME: AGITATION	7	38	
	12	09	10/23/1999	BCDEAA	Complete study	8	42	
	15	10	10/23/1999	DEABCB	Complete study	8	42	
	16	11	10/23/1999	EABCD	Complete study	8	42	
	17	12	10/23/1999	CDEABA	Complete study	8	42	
	18	13	10/23/1999	ABCDEC	Complete study	8	42	
	19	14	10/23/1999	BCDEAD	Complete study	8	42	
	20	15	10/23/1999	ABCDEB	Complete study	8	42	
	Site 4	01	01	10/02/1999	BCDEAC	Complete study	8	42
		02	02	10/02/1999	ABCDEB	Complete study	8	42
		03	03	10/02/1999	EABCDE	Complete study	8	42
		04	04	10/02/1999	BCDEAB	Complete study	8	42
		05	05	10/02/1999	BCDEAA	Complete study	8	42
06		06	10/02/1999	EABCD	Complete study	8	42	
08		08	10/02/1999	DEABCE	Withdrawal of consent	4	16	
09		09	10/02/1999	DEABCE	Complete study	8	42	
10		10	10/02/1999	CDEABC	Complete study	8	42	
11		11	10/02/1999	ABCDEC	Complete study	8	42	

* Last study visit with efficacy information.

** Calculated as the date of last dose minus the date of first dose plus one.

NOTE: A=Placebo B=Adderall 10mg C=SLI381 10mg D=SLI381 20mg E=SLI381 30mg

Generation: 04MAY00

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Table 1.2.1
Randomization and Study Outcome of Individual Subjects by Site
Protocol # 381.201

(Page 3 of 3)

Site	Subject Number	Randomization Number	Randomization Date	Treatment Sequence	Study Outcome	Last Visit*	Time on Drug** (days)
Site 4	12	12	10/02/1999	ABCDED	Complete study	8	42

* Last study visit with efficacy information.

** Calculated as the date of last dose minus the date of first dose plus one.

NOTE: A=Placebo B=Adderall 10mg C=SLI381 10mg D=SLI381 20mg E=SLI381 30mg

Generation: 04MAY00

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