

Final Clinical Study Report

1. TITLE PAGE

Protocol No.: 381.103

Mixed Salts Amphetamine

**A PHARMACOKINETIC STUDY TO COMPARE THE BIOAVAILABILITY
OF A 30 MG SLI381 CAPSULE IN HEALTHY VOLUNTEERS WHEN
ADMINISTERED AS AN INTACT CAPSULE FOLLOWING AN OVERNIGHT
FAST, TO AN INTACT CAPSULE ADMINISTERED WITH FOOD, AND TO AN
OPEN CAPSULE (SPRINKLED ON APPLESAUCE)**

June 27, 2000

<u>Investigator</u>	<u>Site # or Affiliation</u>	<u>Location</u>
Irving E. Weston, MD	MDS Harris	Phoenix, AZ

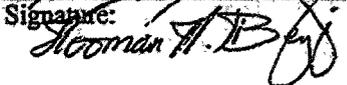
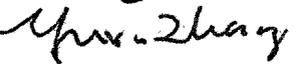
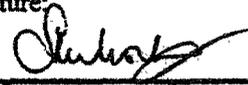
Study Start Date:	December 1, 1999
Study Stop Date:	December 21, 1999

Sponsor:	Shire Laboratories, Inc. 1550 East Gude Road Rockville, MD 20850
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Contact Person:	Yuxin Zhang, PhD
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This study was conducted in compliance with internal review board and informed consent regulations

2. SYNOPSIS

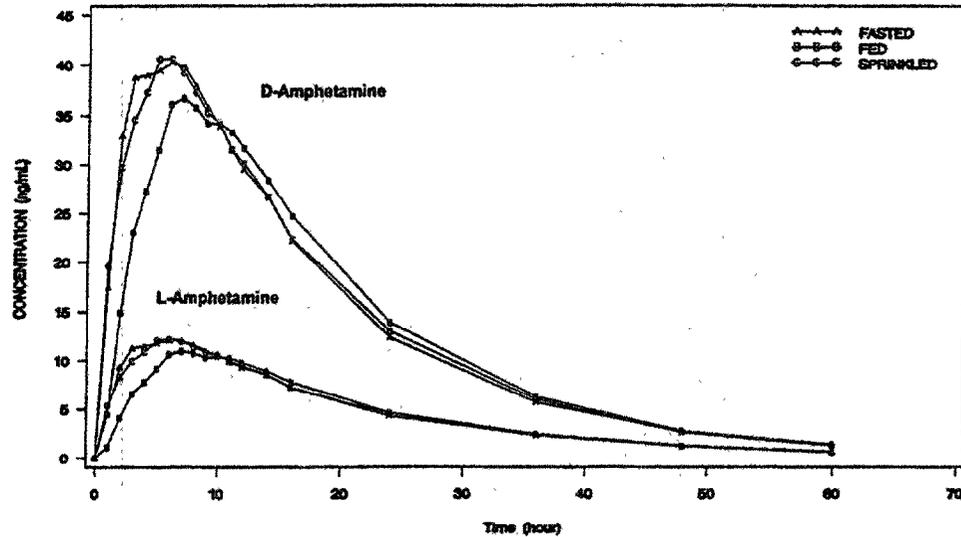
Name of Study Drug: Mixed Salts Amphetamine	IND #: 58,037	Protocol No.: 381.103	Phase: I	Country: USA
Title: A pharmacokinetic study to compare the bioavailability of a 30 mg SLI381 capsule in healthy volunteers when administered as an intact capsule following an overnight fast, to an intact capsule administered with food, and to an open capsule (sprinkled on applesauce)				
Principal Investigator/Affiliation: Irving E. Weston, MD MDS Harris		No. of Study Centers: 1	Study Period: First enrollment date: December 1, 1999 Last completion date: December 21, 1999	
Objectives: To assess the bioequivalence of a single 30 mg dose of SLI381 extended-release capsule administered in applesauce to the same dose administered as an intact capsule with and without a high-fat breakfast. To compare the bioavailability of a single 30 mg dose of SLI381 extended-release capsule administered in fasted state to the same dose administered with a high-fat breakfast.				
Methodology: Study was a randomized, open-label, 3-period, single-dose study with a 7-day washout between each period. The study was a 3-way crossover, with three SLI381 dosing conditions (i.e., intact 30 mg capsule following an overnight fast, intact 30 mg capsule following a high-fat breakfast, contents of a 30 mg capsule sprinkled in one tablespoon of applesauce), during which subjects were randomized to receive one of three dosing conditions in the first study period and alternate dosing conditions in subsequent study periods. Blood samples were collected 5 minutes before drug administration (0 hour, approximately 8:00 am) and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, and 60 hours post-dose. The blood samples were centrifuged within 60 minutes and the separated plasma was stored at or below minus 20°C. Plasma d-amphetamine and l-amphetamine levels were determined by LC/MS/MS method at the Sponsor's lab and the pharmacokinetic parameters were also calculated by the Sponsor. Each subject provided a medical history and underwent a physical examination, and a 12-lead ECG prior to study. Blood and urine were collected for routine clinical laboratory analysis prior to study. Blood pressure and pulse were measured at pre-dose and at 2, 4, and 24 hours post-dose. Urine drug screening test and serum pregnancy test were done during the screening period, and prior to entering each study phase.				
Author: Sally A. Breisch, M.S. for Amarex	Signature: 		Date: 29 June 2000	
Statistician(s): Safety: Hooman Beygi, PhD	Signature: 		Date: 29 June 2000	
Efficacy: Yuxin Zhang, PhD	Signature: 		Date: 30 June 2000	
Approved by: Simon Tulloch, MD SVP, Sponsor's Medical Officer	Signature: 		Date: 7/7/00	

Name of Study Drug:	IND #:	Protocol No.:	Phase:	Country:
Mixed Salts Amphetamine	58,037	381.103	I	USA
<p>Number of Subjects (planned and analyzed): The protocol called for 21 subjects to ensure sufficient statistical power to evaluate (1) the bioequivalence between the intact SLI381 capsule and open/sprinkled SLI381 dosing conditions and (2) the bioavailability of SLI381 intact capsules between the fed and fasted states. Twenty-one subjects participated in the study and twenty subjects completed the study. One subject was withdrawn from the study prior to entering the 2nd period due to taking prescription medication. All data collected from the study participants were evaluated for bioequivalence, bioavailability, and safety.</p>				
<p>Diagnosis and Main Criteria for Inclusion: Healthy volunteers of either sex, 18 to 55 years old, with body weight within $\pm 10\%$ the ideal weight for their gender, height, and estimated frame size.</p>				
<p>Test Product, Dose, Mode of Administration, and Batch Number: Test drug (SLI381 extended-release capsules, lot number 9F2703) was provided by the Sponsor as capsule formulation, each capsule contained 30 mg mixed salts of single entity amphetamine for oral administration.</p>				
<p>Duration of Treatment: This was a single-dose, three-period crossover study with a minimum 7-day washout interval between each dose administration. Dosing time was approximately 8:00 am in the morning of each dosing day.</p>				
<p>Reference Therapy, Dose and Mode of Administration, Batch Number: No real reference therapy was used. For analysis purpose, the fed condition was considered the reference condition.</p>				
<p>Criteria for Evaluation: <u>Efficacy (Pharmacokinetics):</u> Extent (AUC) and rate (C_{max}) of drug absorption and time-to-peak concentration (T_{max}) were evaluated for differences between the dosing conditions using analysis of variance (ANOVA), followed by Dunnett's test for multiple means comparisons. Analysis of bioequivalence was carried out using the ANOVA model with log-transformed data for AUC and C_{max}, and the 90% confidence interval (CI) was constructed for the ratio of the test-to-reference means from the two 1-sided t-tests. The currently used average bioequivalence criteria of 0.80-1.25 limits for log-transformed data were applied to draw conclusions of bioequivalence. <u>Safety:</u> All safety parameters collected were assessed either descriptively and/or comparatively. These parameters included adverse events (AE), clinical laboratory tests (chemistry, hematology, and urinalysis), medical history, physical examinations, 12-lead electrocardiogram (ECG), and vital signs.</p>				
<p>Statistical Methods: <u>Efficacy (Pharmacokinetics):</u> The extent (AUC) and rate (C_{max}) of drug absorption and time-to-peak concentration (T_{max}) were evaluated for differences between dosing conditions using analysis of variance (ANOVA) with a general linear model, followed by Dunnett's test for multiple means comparisons. The ANOVA model included sequence, subject within sequence, period, and condition. The statistical significance level was set at 0.05 for comparative evaluation. Analysis of bioequivalence was carried out using the same ANOVA model with log-transformed data for AUC and C_{max}, and the 90% confidence interval (CI) was constructed for the ratio of the test-to-reference means from the two 1-sided t-tests approach. The currently used average bioequivalence criteria of 0.80-1.25 limits for log-transformed data were applied to draw conclusions of bioequivalence. <u>Safety:</u> Observed adverse events and vital signs were analyzed either descriptively or comparatively using paired t-test for each of the three dosing conditions.</p>				

Name of Study Drug: Mixed Salts Amphetamine	IND #: 58,037	Protocol No. 381.103	Phase: I	Country: USA
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SUMMARY RESULTS
EFFICACY:

Plasma D- and L-Amphetamine Concentration-Time Plot



D-Amphetamine

Condition	Parameters (means)			
	AUC (0-inf) (ng hr/mL)	AUC (0-t) (ng hr/mL)	Cmax (ng/mL)	Tmax (hr)
Fasted	851.17	827.99	44.325 [^]	5.200 [^]
Sprinkled	855.98	834.49	43.514 [^]	5.500 [^]
Fed	822.56	799.28	39.696	7.667
Bioequivalence				
Ratio of fasted-to-fed	1.04	1.04	1.12	
90% CI	0.98-1.10*	0.99-1.10*	1.05-1.18*	
Ratio of sprinkled-to-fed	1.05	1.05	1.10	
90% CI	0.99-1.11*	1.00-1.11*	1.04-1.16*	
Ratio of sprinkled-to-fasted	1.01	1.01	0.99	
90% CI	0.96-1.07*	0.96-1.07*	0.93-1.04*	

L-Amphetamine

Condition	Parameters (means)			
	AUC (0-inf) (ng hr/mL)	AUC (0-t) (ng hr/mL)	Cmax (ng/mL)	Tmax (hr)
Fasted	288.585	271.720	13.323 [^]	5.550 [^]
Sprinkled	290.380	274.645	13.041 [^]	5.600 [^]
Fed	273.557	258.305	11.977	8.333
Bioequivalence				
Ratio of fasted-to-fed	1.05	1.05	1.11	
90% CI	0.99-1.13*	0.99-1.12*	1.05-1.18*	
Ratio of sprinkled-to-fed	1.07	1.07	1.09	
90% CI	1.00-1.14*	1.01-1.14*	1.03-1.16*	
Ratio of sprinkled-to-fasted	1.01	1.02	0.98	
90% CI	0.95-1.09*	0.96-1.08*	0.93-1.04*	

[^] p<0.05 compared to fed condition by Dunnett's test

* Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on log scale

Name of Study Drug:	IND #:	Protocol No.	Phase:	Country:
Mixed Salts Amphetamine	58,037	381.103	I	USA
SUMMARY RESULTS (continued)				
SAFETY:				
All but one subject completed the study as planned. This subject was terminated from the study prior to entering the 2nd study period due to taking a prescription medication for exacerbation of gout.				
The study drug was well-tolerated across the three dosing conditions. Eleven (11) subjects reported a total of 54 adverse events after the start of study drug with one subject reporting 18 events (or 33%). All events were mild or moderate in severity and resolved or improved. Of the 54 reported events, 25 (46%) were unrelated to study medication and 29 (54%) were related or possibly related to study medication. Twenty-three of the 54 reported events (43%) occurred on dosing days and 31/54 events (57%) occurred between dosing days. The event rate was similar between the three dosing conditions, with the fasting and sprinkled conditions having a slightly lower incidence of adverse events than the fed condition.				
Statistically significant increases in mean systolic blood pressure ($p < 0.01$) were observed for the sprinkled condition at 2- and 4-hours post dose. Mean systolic pressure values returned to baseline levels by 24-hours post dose.				
Additionally, statistically significant increases in mean pulse ($p < 0.01$) were noted in all three conditions at 24-hours post dose. Observed mean increases ranged from 10 to 11 beats per minute across the three dosing conditions. The mean changes in pulse at 2-hours post dose were also significantly higher than mean baseline values for the fed and the sprinkled groups.				
CONCLUSIONS:				
The objective of this study was to evaluate the bioequivalence of a single 30 mg dose of SLI381 administered in applesauce (sprinkled) to that of the same dose administered as an intact capsule. Additionally, this study was designed to assess the bioavailability of a single SLI381 30 mg capsule administered after a high-fat meal versus the same dose administered in the fasting state.				
<u>Efficacy</u>				
The study demonstrated that a 30 mg dose of SLI381 administered in applesauce is bio-equivalent in terms of extent (AUC) and rate (C_{max}) of absorption for both d- and l-amphetamine to the same dose administered as an intact capsule in either the fed or the fasting state, based on the current criteria for the 90% CI of the test to reference ratio. The study demonstrated a 30 mg dose of SLI381 administered, as an intact capsule in the fasted state, is bio-equivalent in terms of extent (AUC) and rate (C_{max}) of absorption for both d- and l-amphetamine to the same dose administered in the fed state. The T_{max} was in average about 2 hours shorter for d- isomer and 3 hours shorter for l-isomer when dosed without food or sprinkled on applesauce (otherwise fasted) compared to that when dosed with food.				
<u>Safety</u>				
All formulations were well tolerated. A total of 54 adverse events were observed in the study. A similar incidence of adverse events was noted across the three dosing conditions with the fasted and sprinkled conditions having slightly lower rates than the fed condition.				
No changes in vital signs were found clinically significant. At 2- and 4-hours post dose, statistically significant increases in mean systolic blood pressure were observed for the sprinkled condition; and at 24-hour post dose, statistically significant increases in mean pulse were noted for all three dosing conditions.				
In conclusion, a single 30 mg dose of SLI381 extended-release capsules is bio-equivalent with regard to extend and rate of drug absorption when administered with or without food and when administered as an intact capsule or being sprinkled on applesauce; and, the absorption of both isomers was delayed in the presence of food compared to either fasted or sprinkled on applesauce (otherwise fasted).				

3. TABLE OF CONTENTS

1. TITLE PAGE	I
2. SYNOPSIS	II
3. TABLE OF CONTENTS	1
3.1 LIST OF IN-TEXT TABLES	4
4. GLOSSARY AND DEFINITION OF TERMS	5
5. ETHICS	6
5.1 INSTITUTIONAL REVIEW BOARD (IRB)	6
5.2 ETHICAL CONDUCT OF THE STUDY	6
5.3 SUBJECT INFORMATION AND CONSENT	6
6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE	6
7. INTRODUCTION	6
8. STUDY OBJECTIVES	7
9. INVESTIGATIONAL PLAN	7
9.1 OVERALL STUDY DESIGN AND PLAN	7
9.1.1 Screening	8
9.1.2 Treatment Periods	9
9.2 CHOICE OF CONTROL GROUPS	10
9.3 SELECTION OF STUDY POPULATION	11
9.3.1 Inclusion Criteria	11
9.3.2 Exclusion Criteria	11
9.3.3 Restrictions	11
9.3.4 Removal of Subjects from Therapy or Assessment	12
9.4 TREATMENTS	12
9.4.1 Treatments Administered	12
9.4.2 Identity of Study Drug	12
9.4.3 Method of Assigning Subjects to Treatment Groups	13
9.4.4 Dose Selection	13
9.4.5 Blinding	13
9.4.6 Prior and Concomitant Therapy	12

Final

Date: 27 June 2000

9.4.7	Treatment Compliance	14
9.4.8	Drug Accountability	14
9.5	EFFICACY AND SAFETY VARIABLES	14
9.5.1	Pharmacokinetic Parameters	14
9.5.2	Safety Evaluations	15
9.5.3	Appropriateness of Measurements	16
9.6	DATA QUALITY ASSURANCE	16
9.7	STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE	17
9.7.1	Statistical and Analytical Plans	17
9.7.2	Determination of Sample Size	19
9.8	CHANGES IN THE CONDUCT OF THE STUDY OR THE PLANNED ANALYSES	19
10.	SUBJECT GROUPS	19
10.1	DISPOSITION OF SUBJECTS	19
10.2	PROTOCOL DEVIATIONS	19
11.	EFFICACY EVALUATION	20
11.1	DATA SETS ANALYZED	20
11.2	DEMOGRAPHIC AND OTHER BASELINE CHARACTERISTICS	20
11.3	MEASUREMENTS OF TREATMENT COMPLIANCE	21
11.4	PHARMACOKINETIC (PK) RESULTS	21
11.4.1	D-amphetamine	21
11.4.2	L-amphetamine	23
12.	SAFETY EVALUATION	25
12.1	EXTENT OF EXPOSURE	25
12.2	ADVERSE EVENTS	25
12.2.1	Brief Summary of Adverse Events	26
12.2.2	Number and Percent of Subjects Reporting Adverse Events	26
12.2.3	Analysis of Adverse Events	26
12.3	DEATHS, OTHER SERIOUS ADVERSE EVENTS AND OTHER SIGNIFICANT ADVERSE EVENTS	26
12.3.1	Subjects Withdrawn for Adverse Events	26
12.4	CLINICAL LABORATORY RESULTS	27
12.5	VITAL SIGNS, PHYSICAL FINDINGS, AND OTHER OBSERVATIONS RELATED TO SAFETY	28
12.5.1	Vital Signs	28
12.5.2	Physical Examinations	28
12.5.3	Medical History	29

12.5.4	Other Safety Measures.....	29
12.6	SAFETY CONCLUSIONS.....	29
13.	DISCUSSION AND OVERALL CONCLUSIONS	29
14.	REFERENCED TABLES AND FIGURES NOT INCLUDED IN TEXT	31
15.	REFERENCES	91
16.	APPENDICES	92
	APPENDIX IA: Laboratory Test Reference Values	
	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 SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS 20

TABLE 2 MEAN AND S.D. OF PK PARAMETERS FOR D-AMPHETAMINE 22

TABLE 3 BIOEQUIVALNCE OF PK PARAMETERS FOR D-AMPHETAMINE..... 23

TABLE 4 MEAN AND S.D. OF PK PARAMETERS FOR L-AMPHETAMINE 24

TABLE 5 BIOEQUIVALNCE OF PK PARAMETERS FOR L-AMPHETAMINE 25

4. GLOSSARY AND DEFINITION OF TERMS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ANOVA	Analysis of Variance
AUC	Area Under the Curve
B.I.D.	Twice a day
BP	Blood pressure / Systemic arterial pressure(s)
CFR	Code of Federal Regulations
CI	Confidence Interval
CNS	Central Nervous System
COSTART	Coding Symbols for Thesaurus of Adverse Reaction Terms
CRF	Case Report Form
CRO	Contract Research Organization
DR	Delayed Release
ECG	Electrocardiogram
EDTA	Ethylene Diamine Tetra-acetic Acid
FDA	U.S. Food and Drug Administration
GLM	General Linear Model
Hg	Mercury
HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
IND	Investigational New Drug
IR	Immediate Release
IRB	Institutional Review Board
ITT	Intent-to-Treat
LS Mean	Least Square Mean
mg	Milligram
mL	Milliliter
mm	Millimeter
ng	Nanogram
PI	Principal Investigator
PK	Pharmacokinetic
RBC	Red Blood Cell
SD	Standard Deviation
sec	Second
SOP	Standard Operating Procedure
WBC	White Blood Cell

5. ETHICS

5.1 Institutional Review Board (IRB)

The study protocol, informed consent form (ICF), and any amendments to the protocol were approved by IRBs, prior to study initiation, in conformance with 21 CFR 50 and 21 CFR 56. The approval letters are on file with MDS Harris, the CRO that conducted the study and with the Sponsor. Information about the IRBs is provided in Section 16, Appendix IIC.

5.2 Ethical Conduct of the Study

This protocol was performed under the principles of the 18th World Medical Assembly (Helsinki 1964) and amendments of the 29th (Tokyo 1975), the 35th (Venice 1983) and the 41st (Hong Kong 1989) World Medical Assemblies and 48th General Assembly, Republic of South Africa, October 1996. A copy of this Declaration is in the Investigator file.

5.3 Subject Information and Consent

Each subject signed the Informed Consent Form (ICF) after receiving written information and an explanation of what the study involved. A copy of the Informed Consent Form was given to the subject. Signed and witnessed ICFs are on file at MDS Harris in Lincoln, Nebraska.

6. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted at MDS Harris, Phoenix, AZ, beginning on 01 December 1999 and ending on 21 December 1999 by Irving E. Weston, MD, Principal Investigator (PI). The study was identified by MDS Harris as Protocol 398-04, MDS Harris Project 23369. Name of Investigator(s) and study administrative structure are listed below:

Name and Affiliation	Title	Role
Irving E. Weston, MD MDS Harris 4639 South 36th Street Phoenix, AZ	Principal Investigator	Responsible for study conduct
Cindy Epley, MDS Harris	Project Manager	Management of study
Simon Tulloch, MD, Shire Laboratories Inc	Senior VP, US R&D	Overall responsibility for clinical and safety aspects
Kathleen N. O'Brien, Shire Laboratories Inc	Clinical Program Manager	Sponsor's contact for management of the study

7. INTRODUCTION

Shire Laboratories Inc. has developed a two-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 [1].

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 two 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 two-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.

The purpose of this Phase I study was to assess whether the contents of a single 30 mg dose of SLI381 extended-release capsule formulation administered in applesauce is bioequivalent to the same dose administered as an intact capsule with or without food, and to determine if there is an effect on bioavailability of a single 30 mg dose of SLI381 extended-release capsules administered with a high-fat breakfast compared to the same dose administered in the fasted state in healthy volunteers.

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

8. STUDY OBJECTIVES

To assess the bioequivalence of a single 30 mg dose of SLI381 extended-release capsule formulation administered in applesauce to the same dose administered as an intact capsule with or without food.

To compare the bioavailability of a single 30 mg dose of SLI381 extended-release capsules administered with food (a high-fat breakfast) to the same dose administered without food (in the fasted state).

9. INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan

This trial was a single-dose, randomized, open-label, three-period (or phase) study. It was designed to assess the bioequivalence of a single 30 mg dose of SLI381 extended-release capsule formulation administered in applesauce to that of the same dose administered as an intact capsule with or without food, and to assess the bioavailability of a single SLI381 30 mg extended-release capsule formulation administered in a fasted state versus the same dose administered with a high-fat breakfast.

This was a three-way crossover design. Twenty-one healthy subjects (male and female) were randomized, at study enrollment, to one of the three dose administration sequence groups with seven subjects per group. Subjects were given a single 30 mg dose (1x30

mg) of SLI381 using one of three drug dosing conditions (i.e., intact 30 mg capsule following an overnight fast, intact 30 mg capsule following a high-fat breakfast, or contents of a 30 mg capsule sprinkled in one tablespoon of applesauce) during the first study period and alternate dosing conditions in subsequent study periods.

Subjects were confined to the clinic 10 hours prior to each dosing day. Confinement continued until 24 hours post-dose. Beginning on each dosing day, nineteen (19) blood samples (7 mL per sample) were collected through the 60-hour post-dose interval during each study period for determining the plasma levels of d-amphetamine and l-amphetamine. Blood was collected at the following hours: 0-hour (5 minutes before dosing), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, and 60 hours. Additionally, 15 mL of blood was collected for the screening clinical laboratory evaluation. For females another 15 mL blood (5 mL per check-in period) was collected for pregnancy testing. Dosing for each study period was separated by a seven-day, or greater, washout period.

9.1.1 Screening

Subjects were screened within 21 days before enrollment into the study. All prospective subjects had the study explained to them and signed the IRB approved ICF before study initiation.

Screening measurements included:

- Medical history
- Physical examination
 - Height, weight, and frame size estimation
 - Vital signs (sitting respiratory rate, heart rate, blood pressure, temperature)
 - 12-lead electrocardiogram
- Urinalysis
 - Urine macroscopic measurements:
 - Bilirubin
 - Blood
 - Glucose
 - Ketones
 - Leukocyte esterase
 - Nitrite
 - pH
 - Protein
 - Specific gravity
 - Urobilinogen
 - Urine semi-quantitative microscopic measurements (if protein, leukocytes, nitrite and/or blood were detected):
 - RBC
 - WBC
 - Casts

- Bacteria
- Blood hematology
 - Hemoglobin
 - Hematocrit
 - WBC
 - RBC
 - Platelet count
- Serum chemistry
 - ALT
 - Glucose
 - Creatinine
 - Albumin
 - Thyroxin
- HIV antibody screen
- Serum pregnancy (for females)
- Urine screen for cannabinoids

The Investigator reviewed medical histories, clinical laboratory evaluations, and performed physical examinations. Subjects who met inclusion/exclusion criteria were enrolled into the study.

9.1.2 Treatment Periods

Each treatment period was separated by a minimum seven-day washout interval.

Treatment A: Administration of an intact 1 x 30 mg SLI381 capsule following a minimum 10 hour overnight fast.

Treatment B: Administration of an intact 1 x 30 mg SLI381 capsule following consumption of a high-fat breakfast.

Treatment C: Administration of an opened 1 x 30 mg SLI381 capsule, sprinkled into one tablespoon of applesauce, following a minimum 10 hour overnight fast.

Subjects eligible for study participation were admitted to the clinic in the evening (at least 10 hours) before the scheduled dose. At each treatment period check-in, the subjects completed a brief written questionnaire to affirm that the exclusion criteria/restrictions had not been violated since screening or previous confinement period. Additionally, a urine sample was collected to test for alcohol and drugs of abuse and a blood sample (5 mL) was collected from female subjects for a serum pregnancy test. Subjects remained at the clinic until completion of the 24-hour post-dosing blood collection and returned to the clinic for the 36-, 48-, and 60-hour post-dose specimen collections.

After check-in, each subject received a snack in the evening. All subjects then observed a 10-hour overnight fast.

On the next day (i.e., Day 1 of treatment) subjects randomized to Treatments A and C did not receive breakfast prior to dosing. Subjects randomized to Treatment B received a high-fat breakfast approximately 30 minutes prior to drug administration and completed the meal five minutes prior to dosing. All dosing occurred at approximately 8:00 am.

Standard High-Fat Breakfast (Treatment B)

1 English muffin with butter	2 oz. serving of hash brown potatoes
1 fried egg	8 fluid oz. (240 mL) whole milk
1 slice American cheese	1 slice Canadian bacon

After the morning dose, all subjects fasted for an additional four hours and a standard MDS Harris meal schedule was initiated with lunch at 12:15 pm, dinner at 5:15 pm, and a snack at 9:00 pm. The same menu and meal schedule was administered uniformly for all subjects and was repeated for each study period.

Water was restricted one hour pre-dose to two hours post-dose and food was restricted 10 hours pre-dose to four hours post-dose. During the study, the subjects were not allowed to engage in any strenuous activity. No foods or beverages containing alcohol, ascorbic acid, or caffeine/xanthine were allowed during the confinement period of the study.

For dosing conditions A and B, the study drug (1 x 30 mg dose of SLI381 extended-release capsule formulation) was administered with eight fluid ounces (240 mL) of room temperature tap water. For dosing condition C, a 1 x 30 mg capsule of SLI381 extended-release formulation was opened and sprinkled into one tablespoon of applesauce for administration. A mouth check was performed after dosing to ensure that the dose was swallowed. Subjects were to remain in an upright position (sitting or standing) for four hours after each treatment administration. The subjects were not allowed to engage in any strenuous activity.

Sitting vital signs (blood pressure and pulse) were assessed each morning before dosing and at 2, 4, and 24 hours post-dose.

A total of 19 blood samples (7 mL, EDTA), to be assayed for d-amphetamine and l-amphetamine content by LC/MS/MS method, were collected during each of the treatment periods. Samples were collected at 0-hour (pre-dose), and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, and 60 hours post-dose. Blood samples were stored on ice before plasma was separated by centrifugation (approximately 2500 rpm x 15 minutes at 4°C). All plasma samples were then frozen at -20°C, kept frozen, and packed in dry ice, and sent to Shire Laboratories Inc. at Rockville, Maryland.

Vital signs were monitored throughout the dosing day. Adverse events were assessed via observation and unsolicited reporting.

9.2 Choice of Control Groups

The study was designed to evaluate three dosing conditions. The study did not employ a control group per se. Instead, each subject acted as his/her own control, with the

comparisons being made among the three dosing conditions: administered with food, without food, and capsule opened and contents sprinkled on applesauce.

9.3 Selection of Study Population

The protocol required enrollment of 21 subjects into the study. Subjects were to be non-institutionalized and consisting of college students and members of the community at large.

9.3.1 Inclusion Criteria

Subjects were required to meet the following inclusion criteria:

INCLUSION CRITERIA

1. Male or female between 18 and 55 years of age.
2. Female subjects who were sexually active and of childbearing potential (i.e., not surgically sterile or at least two years post menopausal) were required to use a medically acceptable form of birth control during the study. Acceptable birth control measures were defined as hormonal contraceptives (oral, injectable, or implant), barrier contraceptives (condom, diaphragm with spermicide), IUD, or vasectomized partner (six months minimum).
3. Body weight was to be within $\pm 10\%$ of ideal weight for height and estimated frame size adapted from the 1983 Metropolitan Life Table.
4. No clinically significant abnormal findings on the physical examination, medical history, or clinical laboratory results during screening.
5. Voluntary consent to participate in this study.

Source: Section 16, Appendix II A, Protocol

9.3.2 Exclusion Criteria

Subjects were excluded if they met any of the following exclusion criteria:

EXCLUSION CRITERIA

1. History of allergic or adverse response to amphetamine or any related drug.
2. History of drug or alcohol abuse.
3. History of clinically significant gastrointestinal tract, renal, hepatic, neurologic, hematologic, endocrine, oncologic, pulmonary, immunologic, psychiatric, or cardiovascular disease or any other condition which, in the opinion of the Investigator, would jeopardize the safety of the subject or impact the validity of the study results.
4. Participation in a previous clinical trial within 30 days prior to the study initiation.
5. Blood donation of one pint or more within 30 days prior to study initiation.
6. Plasma donation within seven days prior to study initiation.
7. Abnormal diet or substantial changes in eating habits within 30 days prior to study initiation.
8. Treatment with any known enzyme altering agents (barbiturates, phenothiazines, cimetidine, etc.) within 30 days prior to or during the study.
9. Use of any prescription medicine within 14 days prior to or during the study (excluding hormonal contraceptive or hormonal replacement therapy for females).
10. Use of any over-the-counter medication within seven days prior to or during the study.
11. Pregnant or lactating females.
12. Positive urine screen for alcohol or drugs of abuse.

Source: Section 16, Appendix II A, Protocol

9.3.3 Restrictions

Several restrictions are requested from the participant

Final

Date: 27 June 2000

RESTRICTIONS

1. No consumption of foods or beverages containing alcohol or caffeine/xanthine 48-hours prior to or during each period of confinement.
2. No consumption of any fruit or juices containing ascorbic acid during the periods of confinement.
3. No strenuous exercise or activity during the confinement periods of the study.

Source: Section 16, Appendix IIA, Protocol

9.3.4 Removal of Subjects from Therapy or Assessment

Subjects were advised that they were free to withdraw from the study at any time. Additionally, the Investigator could remove a subject if he felt it was in the best interest of the subject. Appropriate supportive and/or definitive therapy was to be administered to withdrawn subjects, as required.

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. Withdrawn subjects could not re-enter the study.

One subject (#019), a 44-year old, male, American Indian, was withdrawn from the study prior to entering the 2nd period due to taking prescription medication (colchicine and indocin) for exacerbation of gout. This subject received the assigned treatment up the point of withdrawal. All information collected from this subject was assessed for efficacy and safety.

9.4 Treatments

9.4.1 Treatments Administered

At the morning (8:00 am) on Day 1 of periods one through three, the subjects received one of the three treatments (A, B, or C) as illustrated in the table below.

TREATMENTS ADMINISTERED

Treatment Designation	Study Medication	Administration Method
A	SLI381 30 mg capsules	30 mg dose (1 x 30 mg) administered orally with 240 mL of water following a minimum 10 hour overnight fast.
B	SLI381 30 mg capsules	30 mg dose (1 x 30 mg) administered orally with 240 mL of water following a high-fat breakfast.
C	SLI381 30 mg capsules	30mg dose (1 x 30 mg) , capsule opened and contents sprinkled into one tablespoon of applesauce and administered orally, following a minimum 10 hour overnight fast.

9.4.2 Identity of Study Drug

Study drug was supplied in bottles by Shire Laboratories Inc. and shipped to MDS Harris pharmacy, which transferred the study medications into individual unit dose containers for each subject and each study period. Each bottle was identified by lot number, product name, strength, and a precautionary statement.

Treatment	Study Drug	Lot #
A, B, C	SLI381 extended-release 30mg capsules	9F7702

Final
Date: 27 June 2000

The study drug identification was recorded in CRF and is presented in Section 16, Appendix VII Table 1.1.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects were assigned to each treatment according to a randomization schedule prepared for the study by MDS Harris. At the dosing day of each period, subjects received the assigned dose from study personnel. Dosing for each study period was separated by a seven-day or greater washout period. Both the assigned randomized treatment sequence and received treatment sequence for each subject are presented in Section 14, Table 1.1.1, and in Section 16, Appendix VII Table 2.1. The dosing day started on December 5, 1999 for the first period, on December 12 1999 for the second period, and on December 19, 1999 for the third period.

9.4.4 Dose Selection

A 30 mg dose of SLI381 capsule formulation was selected to meet the regulatory requirement since it was the highest strength of the drug product intended for marketing by this submission. The dose was also selected to enable quantitation of anticipated blood levels of both d-amphetamine and l-amphetamine over the 60-hour interval analyzed. Previous experience suggested this dose would be well-tolerated by normal subjects.

9.4.5 Blinding

This was an open-label, crossover trial and the primary endpoints were objective measurements of bioequivalence and bioavailability. Therefore, blinding of subjects, Investigator, or sponsor was not required. The bottles containing drug were clearly labeled as containing 30 mg capsules of SLI381 extended-release formulation.

The treatments administered at each dosing day were recorded in CRF and presented in Section 16, Appendix VII Table 2.1.

9.4.6 Prior and Concomitant Therapy

The protocol stated that, during the course of study, no drugs other than the study medication were to be taken (hormonal contraceptives and hormonal replacement therapy were allowed). Restrictions regarding permitted and excluded medications were identified in the inclusion and exclusion criteria of the protocol.

Concomitant medications taken before and during the study were recorded in CRF and appear in Section 16, Appendix VII Table 3.1. One subject (#002), on and one day before study exit (i.e., after completion of period three), took acetaminophen and/or ibuprofen for elevated temperature. This deviation was allowed by investigator. One subject (#019) took prescription medication (colchicine and indocin) for exacerbation of gout prior to the start of the 2nd study period. This subject was withdrawn from the study at the

check-in of period two. No other concomitant medication violations occurred during the study.

9.4.7 Treatment Compliance

MDS Harris personnel administered each dose of study medication. Time of dose administration was recorded in CRF and is presented in Section 16, Appendix VII, Table 9.1.

To ensure that each dose was taken, a mouth check was performed after drug administration by study personnel. Additionally, subjects were not permitted to lie down for the first four hours following drug administration to ensure proper stomach emptying.

9.4.8 Drug Accountability

Study drug was shipped to MDS Harris by Shire Laboratories Inc. and stored in a locked, limited access area. MDS Harris was responsible for maintenance of cumulative study drug inventory and dispensing records. Drug inventory is presented in the table below.

DRUG INVENTORY				
Treatment	Compound/Dose/Lot Number	Quantity/Date Received	Quantity Spent	Quantity Remaining*
A, B, C	SLI381 capsules / 30mg / 9F2703	300 capsules 03 December 1999	61 capsules	239 capsules

*The remaining inventory was held at MDS Harris as retention samples.

Source: Study documentation binder

9.5 Efficacy and Safety Variables

9.5.1 Pharmacokinetic Parameters

Blood samples were collected for later determination (by LC/MS/MS) of d-amphetamine and l-amphetamine concentrations pre-dosing (5-minutes before dosing) and at the following hours after dosing: 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 14, 16, 24, 36, 48, and 60. From the plasma drug levels, the following parameters for both d-amphetamine and l-amphetamine were measured and calculated for bioavailability and bioequivalence evaluations for each type of dosing administration. Complete details of the assay method and calculation method are provided in Section 16, Appendix VIB: Pharmacokinetic Analytical Report/Technical Report.

Variable	Description
AUC_{0-t}	Area under the drug concentration-time curve from time zero to t hour (t = last measurable concentration time point, C_t), calculated by the trapezoidal rule.
AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity; using $AUC_{0-t} + C_t / K_{el}$ (K_{el} = terminal elimination rate constant)
$t_{1/2}$	Elimination half-life; using $LN(2)/K_{el}$
C_{max}	Maximum observed drug concentration
T_{max}	Time to the maximum drug concentration (obtained without interpolation)

Final

Date: 27 June 2000

9.5.2 Safety Evaluations

The following safety parameters, the primary safety data, were collected throughout the study and were summarized by dosing condition.

- Blood pressure (sitting) (mmHg) and pulse (sitting) (beats/min)
- Adverse events.

Blood pressure and pulse were collected at screening and four times (pre-dose, 2, 4, 24 hours post-dose) on the dosing day of each treatment period.

Adverse event data were obtained by observation during admissions for dosing and blood collection and by unsolicited reporting before, during, and after each dosing and collection phase. Adverse events occurring during this study were to be recorded on the CRF. The Investigator was to review each event and assess its relationship to drug treatment (unrelated, unlikely, possibly, probably, almost certainly). For the purpose of reporting, this drug relationship was collapsed into categories of unrelated (unrelated and unlikely), possibly, and related (probably and almost certainly).

Each reported adverse event was also graded on a 3-point severity scale (mild, moderate, or severe). The severity grading, date and time of onset, time relationship to drug dosing, duration, and outcome of each event were recorded. The following definitions for rating severity were used:

- | | |
|-----------------|--|
| Mild | The adverse event was easily tolerated and did not interfere with daily activity; |
| Moderate | The adverse event interfered with daily activity but the subject was still able to function; |
| Severe | The adverse event was incapacitating and required medical intervention. |

All adverse events, whether serious or non-serious, were to be followed to resolution regardless of whether the subject was still participating in the study. Where appropriate, medical tests and examinations were to be performed to document resolution of event(s). Outcome of each event was classified as resolved, improved, unchanged, worse, fatal, or unknown (lost to follow-up) and recorded on the CRF.

Serious adverse events (as defined by the FDA Code of Federal Regulations (CFR), Chapter 21), whether or not they were deemed to be drug-related, were to be immediately reported by telephone to the Sponsor, followed by a written report within five working days.

Clinical diagnostic and laboratory measures employed to delineate the cause of the reaction in question were to be performed and the results reported. Steps taken to counteract toxic phenomena and the results thereof were to be specified. In all cases of serious or life-threatening reactions, the medication was to be discontinued and any appropriate supportive and definitive therapy given. A full report, including clear

photocopies of hospital records, including consultants' reports, autopsy finding (where appropriate), and a summary of the outcome of the reaction by the Investigator (including his/her opinion of drug relationship or attribution) were to be furnished to Shire Laboratories as soon as practical.

All serious adverse events reported to the FDA were to adhere to 21 CFR 312.32 for IND drugs (7/15-day alerts) and 21 CFR 314.80 for marketed drugs (15-day alerts). The IRB was to be notified of all serious adverse events per FDA regulations.

Other safety data was also collected at either screening period and/or throughout the study. Listings were prepared for any abnormalities observed for these measures, which included the following:

- History
- Physical examination
- Vital signs (sitting respiratory rate, heart rate, blood pressure, temperature)
- 12-lead electrocardiogram
- Urinalysis (macroscopic: bilirubin, blood, glucose, ketones, leukocyte esterase, nitrate, pH, protein, specific gravity, urobilinogen; microscopic if protein, leukocytes, nitrate and/or blood are detected: RBC, WBC, cast, bacterial semi-quantitative measurements)
- Hematology (hemoglobin, hematocrit, WBC, RBC, platelet count)
- Serum chemistry (ALT, glucose, creatinine, albumin, thyroxin)
- HIV antibody screen
- Serum pregnancy (for females at screening and each check-in)
- Urine screen for cannabinoids (at screening and each check-in)
- Urine screen for alcohol and additional drugs (ethanol, amphetamines, opiates, cocaine) at each check-in.

9.5.3 Appropriateness of Measurements

All effectiveness and safety assessments are widely used and generally recognized as reliable, accurate, and relevant. Alternative measures of bioavailability were not considered.

9.6 Data Quality Assurance

MDS Harris was responsible for the conduct of this trial and accuracy of all collected data. The Investigator and staff at MDS Harris are well trained in conducting clinical trials. Protocol specifications and a detailed time and events schedule were prepared by MDS Harris to assure consistent execution of the protocol throughout the study. MDS Harris personnel involved with the study were required to review the portions of the protocol and the time and events schedule that pertained to their role in study conduct. Blank case report forms were developed and reviewed prior to the study. The database construction procedures followed MDS Harris SOPs and the completed CRF were generated from the MDS Harris database after study completion. The Sponsor, according to its SOPs, conducted audits to the study documentation, CRFs, and database. Any errors or omissions discovered after the database was

corrected, initialed, and dated by the Investigator or MDS Harris staff and a new copy of the database was forwarded to the Sponsor.

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

9.7 Statistical Methods and Determination of Sample Size

9.7.1 Statistical and Analytical Plans

Amarex Clinical Research, a CRO located at Gaithersburg, Maryland, prepared a statistical analysis plan (Section 16, Appendix VIA) for the Sponsor, based on protocol-specified analyses.

9.7.1.1 Analyses of Amphetamine Pharmacokinetics

Comparative Analysis of Pharmacokinetic Parameters

Pharmacokinetic (PK) parameters for d-amphetamine and l-amphetamine were first reported using the original metrics. Descriptive statistics (N, mean, median, standard deviation [SD], coefficient of variation [%CV]) of l-amphetamine and d-amphetamine were obtained for all PK parameters by treatment.

Standard analysis of variance (ANOVA) model of a 3-way crossover design with a general linear approach (normal theory) was applied to each of the pharmacokinetic parameters of AUC, C_{max} , and T_{max} . The model included the following factors: sequence, subject-within-sequence, period, and condition. The sequence effect was tested using the patient-within sequence effect, and all other effects were tested using the residual error of the model.

A null hypothesis of zero difference for a parameter under study among the three conditions was assessed at the 0.05 level, with the alternative hypothesis of non-zero differences. For each parameter, the mean values of the fasted and sprinkled conditions were further compared to the fed condition using Dunnett's test with the Type I error rate of 0.05.

Bioequivalence Analysis of Pharmacokinetic Parameters

The extent and rate of drug absorption, as indexed by PK parameters of AUC and C_{max} , were analyzed on log scale, using the same model outlined above to assess the bioequivalence between each pair of dosing conditions. For each PK parameter examined for bioequivalence, the exact outcome obtained from the ANOVA model was tabulated and so was the descriptive statistics. The recommended two one-sided t-test hypotheses for average bioequivalence were tested at the 0.05 level by constructing the 90% confidence interval (CI) of the ratio of the test-to-reference means [2].

9.7.1.2 Analyses of Safety Data

Adverse Events

All adverse events observed in this study, coded by preferred term (COSTART), were listed for individual subjects and tabulated by preferred term with respect to relationship

to study medication and the severity of the adverse event. The frequencies of adverse events and their percentages were reported for all conditions

The adverse events were tabulated descriptively. When the number of adverse events were sufficient to the conduct a statistical test, then the frequencies of adverse events were analyzed comparatively, using either paired t-test and/or Wilcoxon signed rank test, to examine the differences between the fed, fasting, and sprinkled conditions for on-dosing day and off-dosing days, respectively. No adjustments were made for multiple testing. These reported p-values should be interpreted with caution due to testing multiplicity.

Early Termination

Reasons for discontinuation are summarized and tabulated by dosing condition.

Blood Pressure and Pulse

Descriptive statistics summarized the vital signs data at pre-dose and at each time point post-dose. Changes in vital signs from pre-dose to post-dose for each condition were also reported descriptively and analyzed comparatively within each dosing group using paired t-test.

No adjustments were made for multiple testing, and those p-values that were <0.01 were reported in this report.

9.7.1.3 Other Analyses

Demographic and Baseline Characteristics

Descriptive statistics are presented for the following demographic and baseline characteristics by dosing condition:

- Age
- Race
- Sex
- Height
- Weight

All Other Measures

Abnormalities observed at the screening visit are listed in the following measures:

- History
- Physical examination
- Vital signs (sitting respiratory rate, heart rate, blood pressure, temperature)
- 12-lead electrocardiogram
- Urinalysis (macroscopic: bilirubin, blood, glucose, ketones, leukocyte esterase, nitrate pH, protein, specific gravity, urobilinogen; microscopic if protein, leukocytes, nitrate and/or blood are detected: RBC, WBC, cast, bacterial semi-quantitative measurements)
- Hematology (hemoglobin, hematocrit, WBC, RBC, platelet count)
- Serum chemistry (ALT, glucose, creatinine, albumin, thyroxin)
- HIV antibody screen

Abnormalities observed at the screening visit and at the pre-phase check-in are listed in the following measures:

- Serum pregnancy
- Urine screen for cannabinoids
- Urine screen for alcohol and additional drugs (ethanol, amphetamines, opiates, cocaine)

9.7.2 Determination of Sample Size

Findings from previous studies indicated that the estimate of AUC test-to-reference ratio was within the range of 0.90-1.0 for d-amphetamine, and the estimated within-subject-between-formulation σ (log scale) was less than 0.10 for d-amphetamine and less than 0.13 for l-amphetamine.

Given that the true AUC mean for a test condition is within the 90% region of the reference, for a sample size of 18 subjects, the proposed three-way crossover design will have at least 80% power to reject the null-hypothesis of bio-in-equivalence at the 0.05 level.

Based upon these assumptions, the study planned to enroll 21 subjects without replacement.

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

There were no amendments to study protocol. All protocol-specified analyses were conducted.

10. SUBJECT GROUPS

10.1 Disposition of Subjects

Twenty-one (21) subjects were enrolled and randomized to treatment. Twenty (20) subjects completed the study. One subject (#019), a 44-year old male, American Indian, was withdrawn on December 11, 1999 at the check-in of the 2nd Period, due to taking prescription medication (colchicine and indocin) for exacerbation of gout. This subject was assigned to Treatment B (fed dosing condition) in Period 1, which was administered on December 5, 1999.

A listing of individual subject disposition is presented in Section 14, Table 1.1.2 and in Section 16, Appendix VII Table 2.1.

10.2 Protocol Deviations

The following protocol deviations occurred during the conduct of this study:

Subject ID	Deviation
002	Subject took acetaminophen and/or ibuprofen for elevated temperature on and one day before study exit (i.e., after completion of Period 3).
006	No blood sample was collected at the 9-hour ti

Final
Date: 27 June 2000

- venipuncture.
- 007 No blood sample was collected at the 24-hour time point in Period 2 due to a difficult venipuncture.
- 012 Subject's blood pressure at the 24-hour time point, during Period 1, was out of range (141/98). A recheck was not performed.
- 012 No blood sample was collected at the 15-hour time point in Period 2 due to a difficult venipuncture.
- 018 No blood sample was obtained at the 36- and 48-hour time points in Period 3 due to a car accident.
- 019 Subject's blood pressure at the 24-hour time point, during Period 1, was out of range (145/96). The systolic pressure was not recorded.
- 019 Subject took prescription medication (colchicine and indocin) for exacerbation of gout prior to Period 2. Subject was withdrawn from study.
- 020 No blood sample was collected for this subject at the 10-hour time point in Period 1 due to Adverse Event.

11. EFFICACY EVALUATION

11.1 Data Sets Analyzed

The Intent-to-Treat (ITT) population was analyzed for all PK parameters. The ITT population was defined as the set of subjects who were randomized to treatment, received at least one dose of study medication, and the corresponding PK parameters were available. All dosing conditions identified in Section 9.4.1 of this report were assessed.

11.2 Demographic and Other Baseline Characteristics

Table 1 summarizes participating subjects' demographics and other baseline characteristics.

TABLE 1 SUMMARY OF DEMOGRAPHICS AND BASELINE CHARACTERISTICS

Characteristics	Category/Parameters	(Total N=21)
Race (%)	Caucasian	17 (81%)
	Black	2 (10%)
	Hispanic	1 (5%)
	American Indian	1 (5%)
Gender (%)	Male	11 (52%)
	Female	10 (48%)
Height (inches)	Mean	67.9
	SD	4.2
	Median	69
	Min-Max	60-74
Weight (pounds)	Mean	162.0
	SD	30.7
	Median	154
	Min-Max	110-203
Age (years)	Mean	35
	SD	11
	Median	33
	Min-Max	20-53

Source: Section 14 Table 1.1.1

Fifty-two percent (11/21) of subjects enrolled were male and 48% (10/21) were female. Race distribution was primarily Caucasian (81%, 17/21), with two Black subjects (10%), one Hispanic subject (5%), and one American Indian (5%). The ages of study participants

ranged between 20 and 53 years with a mean age of 35 years (s.d.=11). Subjects weighed between 110 and 203 pounds with the mean of 162.0 pounds, and their heights ranged from 60 to 74 inches with the mean of 67.9 inches. Since it was a crossover design, no inferential statistical analyses were conducted on demographic data.

The entry criteria specifically precluded any meaningful differences in other variables (e.g., concomitant illness). A listing of individual subject demographic and baseline characteristics is presented in Section 14, Table 1.1.1.

11.3 Measurements of Treatment Compliance

Treatment compliance was measured by MDS Harris study personnel conducting a mouth check after subjects swallowed the study medications and recorded in the CRF the formulation the subject was taking for a period; and by capsule counts for each study phase and at the end of the study.

Both the assigned treatment sequence and received treatment sequence for subjects are presented in Section 14, Table 1.1.1 and Table 1.1.2.

11.4 Pharmacokinetic (PK) Results

Mean plasma levels (ng/mL) of amphetamine following drug administration are shown in Section 14, Table 2.1.1 for d-isomer and Table 2.2.1 for l-isomer. Data listings of d-amphetamine concentrations and the PK parameters for individual subjects are contained in Section 16, Appendix VII Table 4.1, and data for l-amphetamine are contained in Section 16, Appendix VII Table 4.2.

Graphical representations of mean plasma levels of amphetamine following drug administration are shown in Section 14, Figure 1.1 for all the dosing conditions and both l- and d-amphetamines, Figure 1.2 for d-amphetamine, and Figure 1.3 for l-amphetamine. Graphical presentations of individual subject d- and l-amphetamine concentrations are found in Section 14, Figures 2.1 through 2.3 and Figures 3.1 through 3.3, respectively.

11.4.1 D-amphetamine

Table 2 contains descriptive statistics of each condition for d-amphetamine PK parameters of $AUC_{0-\infty}$, AUC_{0-t} , C_{max} , and T_{max} . The descriptive statistics of each individual subject for d-amphetamine PK parameters of $AUC_{0-\infty}$, AUC_{0-t} , C_{max} , T_{max} and $t_{1/2}$ are provided in Section 14, Tables 2.1.2 through 2.1.6, respectively.

The arithmetic mean and standard deviation of $AUC_{0-\infty}$ (ng•hr/mL) for the fed condition is 822.56 ± 200.18 . For the fasted and the sprinkled conditions, arithmetic mean and standard deviation of $AUC_{0-\infty}$ (ng•hr/mL) are 851.17 ± 213.51 , and 855.98 ± 179.68 , respectively.

The arithmetic mean and standard deviation of AUC_{0-t} (ng•hr/mL) for the fed condition is 799.28 ± 190.50 . For the fasted and the sprinkled conditions, arithmetic mean and standard deviation of AUC_{0-t} (ng•hr/mL) are 827.99 ± 201.96 and 834.49 ± 175.14 , respectively.

TABLE 2 MEAN AND S.D. OF PK PARAMETERS FOR D-AMPHETAMINE

PK parameters	Measures	Fasted	Sprinkled	Fed
AUC_{0-t} (ng hr/mL)	Mean	851.17	855.98	822.56
	S.D.	213.51	179.68	200.18
$AUC_{0-\infty}$ (ng hr/mL)	Mean	827.99	834.49	799.28
	S.D.	201.96	175.14	190.50
C_{max} (ng/mL)	Mean	44.325*	43.514*	39.696
	S.D.	11.104	9.617	8.837
T_{max} (hr)	Mean	5.200*	5.500*	7.667
	S.D.	1.963	1.762	2.309

Source: Section 14, Tables 2.1.2 through 2.1.5

* $p < 0.05$ compared to fed condition by Dunnett's test (Source: Section 14, Table 2.1.8)

The arithmetic mean and standard deviation of C_{max} (ng/mL) for the fed condition is 39.696 ± 8.837 . For the fasted and the sprinkled conditions, arithmetic mean and standard deviation of C_{max} (ng/mL) are 44.325 ± 11.104 and 43.514 ± 9.617 , respectively.

The arithmetic mean and standard deviation of T_{max} (hr) fed condition is 7.667 ± 2.309 . For the fasted and sprinkled conditions, arithmetic mean and standard deviation of T_{max} (hr) are 5.200 ± 1.963 and 5.500 ± 1.762 , respectively.

The ANOVA results of the 3-way crossover for d-amphetamine PK parameters on untransformed data are presented in Section 14, Table 2.1.7. These results indicate there were no statistical differences among the three conditions for AUC_{0-inf} , AUC_{0-t} , and $t_{1/2}$. The significant treatment effects were noted for C_{max} ($p < 0.01$) and T_{max} ($p < 0.001$).

In reference to the fed condition, further multiple means comparisons by Dunnett's test on the raw data disclosed that the differences in either AUC_{0-inf} or AUC_{0-t} were not statistically significant ($p > 0.05$) for the fasted or sprinkled conditions. With respect to C_{max} and T_{max} the differences were statistically significant ($p < 0.05$) for both the fasted and the sprinkled conditions (Section 14, Table 2.1.8). The ANOVA of the 3-way crossover for d-amphetamine PK parameters on log scale are presented in Section 14, Table 2.1.9.

The results of d-amphetamine bioequivalence in the fasted and sprinkled conditions as compared to the fed condition using logarithmic transformations of PK data (AUC_{0-inf} , AUC_{0-t} , and C_{max}) is reported in Table 3 and in Section 14, Tables 2.1.10 and 2.1.11. Additionally, Table 3 and Section 14, Table 2.1.12 display the d-amphetamine bioequivalence results of the sprinkled condition vs. t

Final

Date: 27 June 2000

These results demonstrate that for the fasted and the sprinkled conditions, with reference to fed condition, the 90% confidence intervals of the test-to-reference ratio fell within the recommended 0.80-1.25 limits of average bioequivalence for all three PK parameters. Also, the test-to-reference ratio for the sprinkled vs. the fasted condition fell within the recommended limits of bioequivalence.

Thus, the study demonstrated that when raw data were analyzed, there were no statistically significant differences in either AUC_{0-inf} or AUC_{0-t} for d-amphetamine in the fasted and sprinkled conditions when compared to the fed condition. According to the current criteria of average bioequivalence, the extent (AUC) and rate (C_{max}) of drug absorption for a single 30 mg dose of SLI381 capsule formulation was bioequivalent under the three dosing conditions. However, the T_{max} was, on average, about 2 hours longer for d- isomer in the presence of food, in comparison to that of either fasted state or sprinkled on food.

TABLE 3 BIOEQUIVALNCE OF PK PARAMETERS FOR D-AMPHETAMINE

PK parameters	Measures	Test Condition	
		Fasted	Sprinkled
AUC_{0-inf} (ng hr/mL)	Ratio of test-to-fed condition	1.04	1.05
	90% CI	0.98 – 1.10*	0.99 – 1.11*
AUC_{0-t} (ng hr/mL)	Ratio of test-to-fed condition	1.04	1.05
	90% CI	0.99 – 1.10*	1.00 – 1.11*
C_{max} (ng/mL)	Ratio of test-to-fed condition	1.12	1.10
	90% CI	1.05 – 1.18*	1.04 – 1.16*
AUC_{0-inf} (ng hr/mL)	Ratio of test-to-fasted condition	-	1.01
	90% CI	-	0.96 – 1.07*
AUC_{0-t} (ng hr/mL)	Ratio of test-to-fasted condition	-	1.01
	90% CI	-	0.96 – 1.07*
C_{max} (ng/mL)	Ratio of test-to-fasted condition	-	0.99
	90% CI	-	0.93 – 1.04*

Source: Section 14, Tables 2.1.10 - 2.1.12

* Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on logarithmic scale

11.4.2 L-amphetamine

Table 4 contains descriptive statistics of each condition for l-amphetamine PK parameters of AUC_{0-inf} , AUC_{0-t} , C_{max} , and T_{max} . The descriptive statistics of each individual subject for l-amphetamine PK parameters of AUC_{0-inf} , AUC_{0-t} , C_{max} , T_{max} and $t_{1/2}$ are provided in Section 14, Tables 2.2.2 through 2.2.6, respectively.

The arithmetic mean and standard deviation of AUC_{0-inf} (ng•hr/mL) for the fed condition is 273.557 ± 68.976 . For the fasted and the sprinkled conditions, arithmetic mean and standard deviation of AUC_{0-inf} (ng•hr/mL) are 288.585 ± 79.170 , 290.380 ± 64.487 , respectively.

The arithmetic mean and standard deviation of AUC_{0-t} (ng•hr/mL) for the fed condition is 258.305 ± 64.357 . For the fasted and the sprinkled conditions, arithmetic mean and standard deviation of AUC_{0-t} (ng•hr/mL) are 271.720 ± 72.230 and 274.645 ± 61.295 , respectively.

TABLE 4 MEAN AND S.D. OF PK PARAMETERS FOR L-AMPHETAMINE

PK parameters	Measures	Fasted	Sprinkled	Fed
AUC_{0-t} (ng hr/mL)	Mean	288.585	290.380	273.557
	S.D.	79.170	64.487	68.976
AUC_{0-t} (ng hr/mL)	Mean	271.720	274.645	258.305
	S.D.	72.230	61.295	64.357
C_{max} (ng/mL)	Mean	13.323*	13.041*	11.977
	S.D.	3.660	3.203	2.885
T_{max} (hr)	Mean	5.550*	5.600*	8.333
	S.D.	2.089	1.729	2.887

Source: Section 14, Tables 2.2.2 through 2.2.5

* $p < 0.05$ compared to fed condition by Dunnett's test (Source: Section 14, Table 2.2.8)

The arithmetic mean and standard deviation of C_{max} (ng/mL) for the fed condition is 11.977 ± 2.885 . For the fasted and the sprinkled conditions, arithmetic mean and standard deviation of C_{max} (ng/mL) are 13.323 ± 3.660 and 13.041 ± 3.203 , respectively.

The arithmetic mean and standard deviation of T_{max} (hr) fed condition is 8.333 ± 2.887 . For the fasted and sprinkled conditions, arithmetic mean and standard deviation of T_{max} (hr) are 5.550 ± 2.089 and 5.600 ± 1.729 , respectively.

The ANOVA results of the 3-way crossover for l-amphetamine PK parameters on untransformed data are presented in Section 14, Table 2.2.7. These results indicate there were no statistical differences among the three conditions for AUC_{0-inf} , AUC_{0-t} and $t_{1/2}$. The significant treatment effects were noted for C_{max} ($p < 0.01$) and T_{max} ($p < 0.001$).

In reference to the fed condition, further multiple means comparisons by Dunnett's test on the raw data disclosed that the differences in either AUC_{0-inf} or AUC_{0-t} were not statistically significant ($p > 0.05$) for the fasted or sprinkled conditions. With respect to C_{max} and T_{max} the differences were statistically significant ($p < 0.05$) for both the fasted and the sprinkled conditions (Section 14, Table 2.2.8). The ANOVA of the 3-way crossover for l-amphetamine PK parameters on log scale are presented in Section 14, Table 2.2.9.

The results of l-amphetamine bioequivalence in the fasted and sprinkled conditions as compared to the fed condition using logarithmic transformations of PK data (AUC_{0-inf} , AUC_{0-t} , and C_{max}) is reported in Table 5 and in Section 14, Tables 2.2.10 and 2.2.11. Additionally, Table 5 and Section 14, Table 2.2.12 displays the l-amphetamine bioequivalence results of the sprinkled condition vs. the fasted condition.

These results demonstrate that for the fasted and the sprinkled conditions, with reference to fed condition, the 90% confidence intervals of the test-to-reference ratio fell within the recommended 0.80-1.25 limits of average bioequivalence for all three PK parameters. Also, the test-to-reference ration for the sprinkled vs. the fasted condition fell within the recommended limits of bioequivalence.

TABLE 5 BIOEQUIVALNCE OF PK PARAMETERS FOR L-AMPHETAMINE

PK parameters	Measures	Test Condition	
		Fasted	Sprinkled
AUC _{0-inf} (ng hr/mL)	Ratio of test-to-fed condition	1.05	1.07
	90% CI	0.99 – 1.13*	1.00 – 1.14*
AUC ₀₋₄ (ng hr/mL)	Ratio of test-to-fed condition	1.05	1.07
	90% CI	0.99 – 1.12*	1.01 – 1.14*
C _{max} (ng/mL)	Ratio of test-to-fed condition	1.11	1.09
	90% CI	1.05 – 1.18*	1.03 – 1.16*
AUC _{0-inf} (ng hr/mL)	Ratio of test-to-fasted condition	-	1.01
	90% CI	-	0.95 – 1.09*
AUC ₀₋₄ (ng hr/mL)	Ratio of test-to-fasted condition	-	1.02
	90% CI	-	0.96 – 1.08*
C _{max} (ng/mL)	Ratio of test-to-fasted condition	-	0.98
	90% CI	-	0.93 – 1.04*

Source: Section 14, Tables 2.2.10 - 2.2.12

* Denotes 90% confidence interval fell within the recommended 0.80-1.25 limits of bioequivalence when analyzed on logarithmic scale

Thus, the study demonstrated that when raw data were analyzed, there were no statistically significant differences in either AUC_{0-inf} or AUC₀₋₄ for l-amphetamine in the fasted and sprinkled conditions when compared to the fed condition. According to the current criteria of average bioequivalence, a single 30 mg dose of SLI381 capsule formulation was bioequivalent under the three dosing conditions as indexed by the extent (AUC) and rate (C_{max}) of drug absorption. However, the T_{max} was, on average, about 3 hours longer for l-isomer in the presence of food, in comparison to that of either fasted state or sprinkled on food.

12. SAFETY EVALUATION

12.1 Extent of Exposure

All 21 subjects received one single oral dose of 30 mg as an intact capsule in the fed state (Treatment B). Twenty subjects received one single oral dose of 30 mg as an intact capsule in the fasted state (Treatment A) and 20 subjects received the contents of one single 30 mg capsule sprinkled over applesauce (Treatment C). The three treatment periods were each separated by one week.

12.2 Adverse Events

Section 14 contains detailed listings and summarization of the adverse events reported during this study. A guide to these tables is provided in the listing below.

Final

Date: 27 June 2000

Table #	Title
3.1.1	Adverse Events Recorded in CRF by Individual Subjects
3.1.2	Adverse Events Recorded in CRF by Study Phase
3.1.3	Adverse Events by Costart Label in Relation to Severity and Treatment
3.1.4	Adverse Events by Costart Label Reported by Individual Subjects
3.2.1	Number (%) of Subjects Reporting Adverse Events by Costart Label: All Treatments
3.2.2	Number (%) of Subjects Reporting Adverse Events by Costart Label: Fasted State
3.2.3	Number (%) of Subjects Reporting Adverse Events by Costart Label: Fed State
3.2.4	Number (%) of Subjects Reporting Adverse Events by Costart Label: Sprinkled State
3.3.1	Adverse Events Observed During Treatment Period (Including Dosing Day)
3.4.1	Adverse Events Observed On Dosing Day
3.5.1	Adverse Events Observed Off Dosing Day

12.2.1 Brief Summary of Adverse Events

Eleven (11) subjects reported a total of 54 adverse events after the start of study drug with one subject (#018, a 45-year old white female) reporting 18 events (or 33% of total reported events). All events were mild (94%, 51/54) or moderate (6%, 3/54) in severity and resolved or improved. Of the 54 reported events, 25 (46%) were unrelated to study medication and 29 (54%) were related or possibly related to study medication. Twenty-three of the 54 reported events (43%) occurred on dosing days and 31/54 events (57%) occurred between dosing days. The event rate of percent patients reporting adverse events was similar between the three dosing conditions, with the fasting condition (20%) and sprinkled condition (25%) having a slightly lower incidence of adverse events than the fed condition (33%).

12.2.2 Number and Percent of Subjects Reporting Adverse Events

The number of events (related and unrelated) and the number and percentage of subjects reporting events are shown in Table 6 by dosing condition. Under the fed condition 7/21 (33%) of subjects reported one or more adverse events, while under the fasted and sprinkled conditions, 4/20 (20%) and 5/20 (25%) subjects, respectively, reported one or more adverse events. For the three conditions, fed, fasted and sprinkled, the total number of adverse events reported per condition was 22, 14, and 18, respectively. These results showed that the fasted and sprinkled dosing conditions did not elicit more adverse events than the fed condition.

12.2.3 Analysis of Adverse Events

No statistical comparisons were conducted on adverse events as most events occurred at a frequency of one to three events per dosing condition except insomnia (4) in the fed condition.

12.3 Deaths, Other Serious Adverse Events and Other Significant Adverse Events

12.3.1 Subjects Withdrawn for Adverse Events

No subjects were withdrawn for this study for adverse events. No deaths or other serious adverse events occurred during this study.

TABLE 6 NUMBER AND % OF SUBJECTS REPORTING ADVERSE EVENTS

Treatment	Preferred Term (COSTART)	No. Subjects Reporting	% Subjects Reporting	No. AE reported
Fasted (n=20)	Diarrhea	1	5	1
	Dizziness	2	10	3
	Dry Mouth	2	10	2
	Epistaxis	1	5	1
	Headache	2	10	2
	Insomnia	1	5	1
	Nausea	2	10	3
	Vasodilation	1	5	1
	Total:	4	20	14
Fed (n=21)	Dizziness	1	5	1
	Ecchymosis	1	5	2
	Gout	1	5	1
	Headache	2	10	3
	Insomnia	4	19	4
	Myalgia	1	5	1
	Nausea	1	5	2
	Pain	2	10	3
	Pharyngitis	1	5	1
	Pruritis	1	5	1
	Rash	1	5	2
	Vomit	1	5	1
	Total:	7	33	22
Sprinkled (n=20)	Chills	1	5	1
	Cough Increased	1	5	1
	Dizziness	2	10	2
	Dyspnea	1	5	1
	Fever	1	5	1
	Headache	3	15	3
	Insomnia	2	10	2
	Lung Dis	1	5	1
	Nausea	3	15	3
	Pain	1	5	1
	Rhinitis	1	5	1
	Thinking Abnormal	1	5	1
	Total:	5	25	18

Source: Section 14 Tables 3.2.2 through 3.2.4

12.4 Clinical Laboratory Results

A listing of all laboratory results for individual subjects is found in Section 16, Appendix VII Table 5.1 (hematology), Table 5.2 (serum chemistry), Table 5.3 (urinalysis), Table 5.4 (urine drug screen), and Table 5.5 (pregnancy). Hematology, serum chemistry, and urinalysis test were obtained at the screening visit only. Urine drug screen and pregnancy tests were collected at screening and at each pre-study check in.

All observed hematology, chemistry, and urinalysis abnormalities are listed in Section 14, Table 4.1.1. There were four abnormal laboratory test values at screening from 2 subjects as outlined below:

Subject ID	Sex	Abnormality	Normal Range
014	F	Bacteriuria: Trace	Negative
020	F	Hematocrit: 44.1%	31.9% – 43.6%
		Hemoglobin: 15.0 g/dL	10.9 g/dL – 14.6g/dL
		Total RBC Count: 5.07 mil/ μ L	3.5 mil/ μ L – 5.05 mil/ μ L

All abnormalities observed at the screening visit were just slightly outside the upper limits of normal. All pregnancy tests were negative. All urine drug screens were negative.

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

12.5.1 Vital Signs

During each treatment period, blood pressure and pulse were measured at pre-dose and at 2-, 4-, and 24-hours post-dose. Descriptive statistics of mean values and mean changes from pre-dose to each time point post-dose by dosing condition are displayed in Section 14, Tables 5.1.1 through 5.1.3 for systolic blood pressure, diastolic blood pressure, and pulse, respectively. Vital signs data for individual subjects are displayed in Section 16, Appendix VII Table 6.1.

Compared to pre-dose, a significant increase in pulse ($p < 0.01$) at 24 hours post-dose was noted for all three dosing conditions. Additionally, a significant increase ($p < 0.01$) in systolic blood pressure was noted at 2 and 4 hours post-dose for the sprinkled dosing condition. No significant increases in diastolic blood pressure were noted. None of the changes in blood pressures or pulse were deemed by Investigators as clinically significant.

Systolic Blood Pressure

At the $p = 0.01$ level, a statistically significant increase in changes from pre-dose to post-dose were observed in systolic blood pressure for the sprinkled dosing condition (at 2- and 4-hours post-dose). By 24-hours post-dose, the mean systolic blood pressure values for this dosing condition returned to baseline level.

Diastolic Blood Pressure

At the $p = 0.01$ level, no statistically significant increases in changes from pre-dose to post-dose were observed in diastolic blood pressure for any of the dosing conditions.

Pulse

At the $p = 0.01$ level, a statistically significant increase in change from pre-dose to 24-hours post-dose was observed in pulse for all three dosing conditions. The average change from baseline at this time point ranged from 10 to 11 beats per minute for the three groups. Additionally, significant changes from pre-dose to 2-hours post dose were noted for the fed and the sprinkled groups. Average increases at 2-hours post dose for the fed group were approximately 8 beats per minute and approximately 7 beats per minute for the sprinkled group.

12.5.2 Physical Examinations

Physical examinations were performed on all subjects at the screening visit. Results are displayed in Section 14, Table 6.1.1. Physical examination findings for all body systems were normal with the exception of seven subjects with abdominal scars and one subject presenting with a slight sag at the lower corner of the mouth that was deemed by the investigator as not clinically significant.

12.5.3 Medical History

Medical histories were collected from all subjects at the screening visit. A listing of medical history abnormalities appears in Section 14, Table 7.1.1. Fourteen of 21 subjects reported one or more medical history abnormalities. Significant and/or continuing abnormalities included smoking, allergies (pet dander, codeine, penicillin, seasonal, sulfa), asthma, arthritis, irritable bowel syndrome, persistent sinus problems, tinnitus, hepatitis A/jaundice (resolved one year prior to study participation), spleen disorder (resolved 2 years prior to study participation), uterine disorder (resolved 1 year prior to study participation), bells palsy, and gout. All medical history abnormalities were deemed not clinically significant by the investigator.

12.5.4 Other Safety Measures

A 12-lead ECG was conducted on each subject at the screening visit. ECG data for individual subjects are displayed in Section 16, Appendix VII Table 7.1. Five of the 21 subjects enrolled in the trial had a reported abnormality that was within normal range or was judged by the investigator as clinically insignificant.

12.6 Safety Conclusions

All formulations were well tolerated. A total of 54 adverse events were observed in the study. A similar incidence of adverse events was noted across the three dosing conditions with the fasted and sprinkled conditions having slightly lower rates than the fed condition.

Statistically significant increases in mean systolic blood pressure ($p < 0.01$) were observed for the sprinkled condition at 2- and 4-hours post dose. Mean systolic pressure values returned to baseline levels by 24-hours post treatment. These changes were not deemed to be clinically significant.

Additionally, statistically significant increases in mean pulse ($p < 0.01$) were noted in all three groups at 24-hours post dosing. Observed mean increases ranged from 10 – 11 beats per minute across the three dosing conditions. The mean changes in pulse at 2-hour post dose were also significantly higher than mean baseline values for the fed and the sprinkled treatments. These changes were not deemed to be clinically significant.

13. DISCUSSION AND OVERALL CONCLUSIONS

Shire Laboratories Inc. has developed a two-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).

The objective of this study was to evaluate the bioequivalence of a single 30 mg dose of SLI381 administered in applesauce to that of the same dose administered as an intact capsule. Additionally, this study was designed to assess the bioavailability of a single

SLI381 30 mg capsule administered after a high-fat meal versus the same dose administered in the fasting state.

Efficacy

The study demonstrated that a 30 mg dose of SLI381 administered in applesauce is bioequivalent in terms of extent (AUC) and rate (C_{max}) of absorption for both d- and l-amphetamine to the same dose administered as an intact capsule in either the fed or the fasting state; and, a 30 mg dose of SLI381 administered, as an intact capsule in the fasted state, is bioequivalent in terms of extent (AUC) and rate (C_{max}) of absorption for both d- and l-amphetamine to the same dose administered in the fed state.

The T_{max} was found to be, on average, about 2 hours longer for d-isomer and 3 hours longer for l-isomer in the presence of food, compared to that of either fasted state or sprinkled on applesauce (otherwise fasted). Thus, the absorption of both isomers appears to have been delayed in the presence of food. These observations are consistent with published work describing an increase in time for gastric emptying in the presence of food.

Safety

All but one subject completed the study as planned. This subject was terminated from the study prior to entering the 2nd study period due to taking a prescription medication.

The study drug was well tolerated across the three dosing conditions. Eleven (11) subjects reported a total of 54 adverse events after the start of study drug. All events were mild or moderate in severity and resolved or improved. Of the 54 reported events, 25 (46%) were unrelated to study medication and 29 (54%) were related or possibly related to study medication. Twenty-three of the 54 reported events (43%) occurred on Dosing Days and 31/54 events (57%) occurred between Dosing Days. The event rate was similar between the three dosing conditions, with the fasting and sprinkled conditions having a slightly lower incidence of adverse events than the fed condition.

Statistically significant increases in mean systolic blood pressure ($p < 0.01$) were observed for the sprinkled condition at 2- and 4-hour post dose. And statistically significant increases in mean pulse ($p < 0.01$) were noted in all three groups at 24-hour post dosing.

In conclusion, a single 30 mg dose of SLI381 extended-release capsules is bio-equivalent with regard to extent and rate of drug absorption when administered with or without food and when administered as an intact capsule or being sprinkled on applesauce; and, the absorption of both isomers was delayed in the presence of food compared to either fasted or sprinkled on applesauce (otherwise fasted).