Exhibit A

Shire

CLINICAL STUDY REPORT

STUDY NO: SLI381-111

A Phase 1 Study to Assess the Relative Bioavailability of Single 30mg Doses of ADDERALL XR® Capsules and ADDERALL® Tablets vs. an Oral Solution of Mixed Amphetamine Salts (MAS) in Healthy Adult Volunteers Aged 18-55

Generic Name:	**ADDERALL XR® (formerly known as SLI381) a once daily extended-release, single-entity amphetamine product**
Indication:	Attention Deficit Hyperactivity Disorder
Phase of Study:	I
Principal Investigator:	Carlos A. Fierro, MD PRA International Clinical Pharmacology Center 16300 College Boulevard Lenexa, Kansas 66219 USA
Study Start Date: **Study Completion Date:**	28 June 2005 (first subject enrolled) 01 Sept 2005 (last subject completed follow-up)
Sponsor:	Shire Development Inc, 725 Chesterbrook Boulevard Wayne, Pennsylvania 19087 USA
Name of Sponsor's Medical Officer:	Timothy Whitaker, MD
Signature	11/30/05

This study was performed according to the protocol and in compliance with Good Clinical Practices (GCP)

Report Date:	30 November 2005 Version 1.0
Previous Versions:	None

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SYNOPSIS

Study number: SLI381-111	**Study drug:** ADDERALL XR® (formerly known as SLI381)

Title of the study: A Phase 1 Study to Assess the Relative Bioavailability of Single 30mg Doses of ADDERALL XR® Capsules and ADDERALL® Tablets vs. an Oral Solution of Mixed Amphetamine Salts (MAS) in Healthy Adult Volunteers Aged 18-55

Investigator:
Principal Investigator: Carlos A. Fierro, MD

Study center:
PRA International Clinical Pharmacology Center
Lenexa, KS 66219

Publications (reference):

None

Study period: 28 June 2005 to 01 Sept 2005	**Clinical phase:** I

Objectives:

Primary

The primary objective of this study was to assess the relative bioavailability of single 30mg doses of Adderall XR capsules and Adderall tablets versus an oral solution of MAS [5mg/mL].

Secondary

The secondary objective of this study was to describe the safety profile of single 30mg doses of Adderall XR capsules, Adderall tablets, and an oral solution of MAS [5mg/mL].

Methodology:

This research study utilized a randomized, open-label, single-dose, three-period, six-sequence crossover design.

Screening/Washout:

Subjects were to be screened up to 2 weeks prior to randomization. After obtaining informed consent, screening procedures (including 12-lead electrocardiogram [ECG] and collection of blood and urine) to determine subject eligibility were to take place. Subjects taking medication(s) at Screening were to begin washout as instructed by the Investigator, if applicable.

Check-in for Periods 1-3:

Subjects were to be admitted to the clinic on the evening of Day -1 of each Check-in Period for confirmation of eligibility. Subjects were to be given a standard meal approximately 12 hours prior to dosing and commence fasting at least 10 hours prior to dosing.

Treatment Periods 1-3:

Prior to the first dosing, all subjects were to be randomly assigned to one of 6 treatment sequence groups. Subjects were to receive their assigned treatment (a single oral 30mg dose of Adderall XR capsules, Adderall tablets, or 6mL of an oral solution of MAS [5mg/mL] after an overnight fast. Vital signs (blood pressure [BP] and heart rate [HR]) were to be taken at predose (0 hour), every hour for the first 12 hours, and at 24, 48, and 60 hours postdose. Electrocardiograms were to be taken at predose (0 hour), every 45 minutes for the first 6 hours, every 1.5 hours for the next 6 hours, and at 24, 48, and 60 hours postdose. Blood draws were to be taken at predose (0 hour), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 14, 24, 48, and 60 hours postdose.

Subjects may have been released from the inpatient unit after completion of the 24-hour postdose assessments but all were required to return to the clinic for 48- and 60-hour postdose assessments.

There was to be a 1-week washout between Treatment Periods.

End of study procedures were to be conducted as part of the 60-hour assessments for Treatment Period 3.

Follow-up:

A follow-up telephone contact was to be conducted approximately 30 days (±5 days) following each subject's last

dose of study medication to collect information on ongoing adverse events (AEs) and serious adverse events (SAEs) and to collect any new related AEs and new onset SAEs.

Number of subjects (total and for each treatment arm):

Eighteen (18) subjects were planned to be enrolled in the study. There were six treatment sequences. Each treatment sequence group consisted of three subjects. A total of 18 subjects were enrolled and randomized to the study and 17 subjects completed their randomized treatment sequences. Eighteen subjects are included in the Safety population and Pharmacokinetic (PK) population.

Diagnosis and main criteria for admission:

Study subjects were to be healthy volunteers of either sex, 18 to 55 years old, with body mass index (BMI) of 20-29 kg/m^2. Subjects' ECG results should have been within normal ranges as judged by the centralized reader. Subjects must also have had clinical laboratory evaluations within the normal reference ranges for the test laboratory, unless deemed not clinically significant by the Investigator.

Test product, dose and mode of administration, batch no.:

Adderall XR is a capsule formulation designed for once-a-day oral administration of mixed salts of a single-entity amphetamine. Adderall XR 30mg capsules were used for this study.

Batch Number: A07566A

Adderall is an immediate release tablet formulation designed for administration of mixed salts of a single-entity amphetamine. Adderall 30mg tablets were used for this study.

Batch Number: A07494A

Duration of treatment:

- Screening and prestudy washout period: approximately 2 weeks
- Treatment period: 3 weeks
- Follow-up: 30 days (±5 days)

Eligible subjects were to visit the clinic approximately 7 times over the course of approximately 5 weeks. At approximately 30 days (±5 days) post-discontinuation or completion of study drug, a follow-up telephone contact was to occur to collect information on ongoing AEs and SAEs and to collect any new related AEs and new onset SAEs.

Reference therapy, dose and mode of administration, batch no.:

An oral solution of 6mL MAS [5mg/mL] was used for this study.

Batch/Lot Numbers of the MAS:

Amphetamine Sulfate, United States Pharmacopeia (USP) CII=A10753

Dextroamphetamine Sulfate, USP CII=A12184

Amphetamine Aspartate, CII=A11900

Dextroamphetamine Saccharate, CII=A12339

Criteria for evaluation:

Pharmacokinetic: *d*- and *l*-amphetamine concentrations were to be determined in plasma samples collected at the following times: predose (0 hour), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 14, 24, 48, and 60 hours postdose for each treatment. Plasma *d*- and *l*-amphetamine concentrations were to be measured with a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method.

Safety: Safety measures were to include the collection of AEs, clinical laboratories, physical examinations, weight, temperature, vital signs (systolic and diastolic BP, HR, and sitting respiratory rate), and ECGs.

Statistical methods:

Pharmacokinetic:

Pharmacokinetic parameters were to be summarized by treatment using descriptive statistics. AUC_{0-t}, $AUC_{0-\infty}$ and C_{max} were to be compared among treatments using a mixed model analysis of variance of the natural log-transformed PK parameters with a random term for subject-within-sequence and fixed terms for sequence, period, and treatment. Confidence intervals (90%) were to be constructed for the exponentiated least squares means ratios of Adderall and Adderall XR compared to the solution. Bioequivalence between treatments was to be declared if the 90% confidence intervals were within the 80-125% range.

The following parameters were to be calculated for *d*- and *l*-amphetamine using noncompartmental analysis:

AUC_{0-t}, $AUC_{0-\infty}$, $t_{1/2elim}$, C_{max}, t_{max}, CL/F, and Vz/F: The latter two parameters were to be calculated with and without correction for body weight. The PK parameters were defined as follows:

- AUC_{0-t}: Area under the drug concentration-time curve from time zero to the time of the last quantifiable plasma concentration obtained by the linear trapezoidal method.
- $AUC_{0-\infty}$: Area under the drug concentration-time curve from time zero to infinity, calculated as $AUC_{0-\infty} = AUC_{0-t} + C_t/\lambda_z$, where λ_z is the terminal phase elimination rate constant.
- $t_{1/2elim}$: Terminal elimination half-life calculated as $Ln(2)/\lambda_z$.
- C_{max}: Maximum observed plasma concentration.
- t_{max}: Time of occurrence of C_{max}
- CL/F: Apparent oral clearance calculated as drug dose divided by $AUC_{0-\infty}$
- Vz/F: Volume of distribution calculated as drug dose divided by $[\lambda_z \times AUC_{0-\infty}]$

Safety: Adverse events were coded using the Medical Dictionary for Regulatory Activities (MedDRA) version 8.0 adverse event dictionary. The frequency of treatment-emergent adverse events (TEAE) was tabulated by body system and preferred term for each treatment. Adverse events were further summarized by severity and relationship to study drug. Adverse events leading to study withdrawal were summarized separately by body system, preferred term, and treatment period.

Clinical laboratory evaluations were summarized by treatment and visit. Hematology and biochemistry were summarized using descriptive statistics; discrete urinalysis measurements were summarized using frequencies and percents, and continuous urinalysis measurements were summarized using descriptive statistics. Shifts in laboratory evaluations from Screening to End of Study were summarized by analyte. Potentially clinically important laboratory outliers were summarized by analyte and visit based on criteria provided in Section 5.7.1.2.

Vital signs, including HR, systolic and diastolic BP, and respiration rate, were summarized by treatment for each measured time point using descriptive statistics. Change from Baseline was also calculated and summarized for each postbaseline time point. The incidence of vital sign outliers was summarized by time point and treatment.

Electrocardiogram parameters were summarized by treatment for each measured time point using descriptive statistics. Change from Baseline was also calculated and summarized for each postbaseline time point. The incidence of ECG outliers was summarized by time point and treatment.

Prior and concomitant medications and physical examination data were listed.

Summary – Results:

Subject demographics: The overall gender distribution was 78% (14/18) males and 22% (4/18) females. The overall racial distribution was 78% (14/18) White, 17% (3/18) Black/African-American, and 6% (1/20) having a race categorized as other. The age of the study subjects ranged from 21-52 years with an overall mean age (standard deviation [SD]) of 34.0 years (10.91). Subjects weighed between 50kg and 93kg with a mean weight (SD) of 73.9kg (11.14), and height ranged between 152cm-193cm with a mean height (SD) of 173.9cm (10.57). Body Mass Index ranged between 20.4kg/m^2-28.5kg/m^2 with a mean BMI (SD) of 24.4 (2.21).

Pharmacokinetic results:

Synopsis Table I: Plasma Pharmacokinetic Parameters for *d*- and *l*-Amphetamine Following a Single 30mg Amphetamine Dose

Parameters	Adderall XR (A)		Adderall (B)		MAS (C)		Ratio of LS Means		90% CI	
	Mean (±SD)	LS Mean	Mean (±SD)	LS Mean	Mean (±SD)	LS Mean	A/C	B/C	A/C	B/C
d-Amphetamine										
C_{max} (ng/mL)	44.0 (7.3)	43.4	46.2 (10.4)	45.2	45.4 (8.7)	44.7	97.1	101.0	92.5, 101.9	96.2, 106.0
T_{max}* (hr)	5.0 (2.5, 10.0)		2.5 (2.0, 4.0)		3.0 (2.0, 4.5)					
$AUC_{0-\infty}$ (hr*ng/mL)	843.8 (120.0)	836.4	844.1 (102.3)	839.2	838.8 (136.3)	830.9	100.7	101.0	96.3, 105.2	96.6, 105.6
AUC_{0-t} (hr*ng/mL)	821.7 (118.4)	814.4	825.1 (100.7)	820.7	820.4 (135.5)	813.1	100.2	100.9	95.9, 104.6	96.7, 105.4
l-Amphetamine										
C_{max} (ng/mL)	14.0 (2.5)	13.8	14.6 (3.2)	14.3	14.3 (2.8)	14.1	97.7	101.6	92.8, 102.9	96.5, 106.9
T_{max}* (hr)	5.0 (3.0, 10.0)		2.5 (2.0, 10.0)		3.0 (2.5, 4.5)					
$AUC_{0-\infty}$ (hr*ng/mL)	315.2 (51.9)	311.6	318.5 (49.1)	314.2	318.0 (61.3)	312.4	99.7	100.6	94.9, 104.8	95.7, 105.7
AUC_{0-t} (hr*ng/mL)	297.3 (49.6)	294.2	302.2 (46.6)	298.5	302.3 (59.7)	297.3	99.0	100.4	94.3, 103.9	95.6, 105.4

LS=Least squares
SD=Standard deviation
* T_{max} presented as Median (min, max)
(A) Adderall XR 30mg
(B) Adderall 30mg
(C) MAS [5mg/mL] x 6mL

- The exposures to both *d*- and *l*-amphetamine as assessed by C_{max} and AUC values from healthy subjects following a dose of either Adderall XR or Adderall was comparable to the exposure after MAS treatment. The 90% confidence intervals for the ratios of least squares (LS) means were contained entirely within the typically accepted bioequivalence range of 80-125%.
- In comparing plasma concentration-time profiles, time to maximum plasma concentrations of both the *d*- and *l*-isomers was comparable between Adderall and MAS treatments. However, C_{max} occurred approximately 2 hours later for the Adderall XR treatment.
- The Vz/F and CL/F of both *d*- and *l*-amphetamine was similar during the Adderall XR, Adderall, and MAS treatment periods.

Safety results:

Adverse events: Seventeen of 18 subjects (94.4%) reported one or more TEAEs during the study. A total of 73 TEAEs were reported. Thirteen of 18 subjects (72.2%) reported 25 TEAEs after receiving Adderall XR, 11 of 17 subjects (64.7%) experienced 16 TEAEs after receiving Adderall, and 12 of 17 subjects (70.6%) experienced 32 TEAEs after receiving MAS. The percentage of subjects reporting a TEAE was generally similar after receiving Adderall XR (72.2%), Adderall (64.7%), and MAS (70.6%). The most common TEAEs were contact dermatitis

(4/18, 22.2% for Adderall XR; 1/17, 5.9% for Adderall; and 3/17, 17.6% for MAS), palpitations (2/18, 11.1% for Adderall XR; 2/17, 11.8% for Adderall; and 3/17, 17.6% for MAS), and dry mouth (1/18, 5.6% for Adderall XR; 2/17, 11.8% for Adderall; and 2/17, 11.8% for MAS). All instances of contact dermatitis were located on the chest and related to ECG lead placement. All contact dermatitis AEs were not suspected to be related to study drug.

Forty of the 73 reported TEAEs (54.8%) were considered by the Investigator as having a suspected relationship to study drug. The Investigator considered all other TEAEs as not suspected to be related (33/73, 45.2%) to study drug. The most commonly reported TEAEs that were considered as having a suspected relationship to study drug were palpitations, dry mouth, hypervigilance, and vision blurred. The percentage of subjects with treatment-emergent palpitations was higher following MAS (17.6%) treatment in comparison to the Adderall XR (11.1%) and Adderall (11.8%) treatment periods. The percentage of subjects with treatment-emergent dry mouth was higher during the Adderall (11.8%) and MAS (11.8%) treatment periods in comparison to the Adderall XR (5.6%) treatment period. The percentage of subjects with treatment-emergent hypervigilance was higher following MAS (17.6%) treatment in comparison to the Adderall XR (0.0%) and Adderall (5.9%) treatment periods. The percentage of subjects with treatment-emergent vision blurred was higher during the Adderall XR (11.1%) treatment period in comparison to the Adderall (0.0%) and MAS (5.9%) treatment periods.

The majority of TEAEs were considered by the Investigator to be mild (59/73, 80.8%) in intensity. All AEs resolved before the subject was discharged from the study.

Deaths, serious adverse events, and withdrawals due to adverse events: No subject died or reported a SAE. One subject (1-419) was withdrawn from the study due to an adverse event of ECG ST-T segment abnormalities following treatment with Adderall XR. Subsequent central over-read of the ECGs by a cardiologist found the ECGs to be normal.

Clinical laboratory evaluations: There were no clinically meaningful differences between the Adderall XR, Adderall, or MAS treatment periods in mean hematology, chemistry, or urinalysis assessments. There were no clinically significant treatment-emergent abnormal laboratory values and no laboratory adverse events.

Physical examination: No clinically significant physical examination findings were noted by the Investigator.

Vital signs: Mean systolic BP increased relative to Baseline at all postdose time points in during the Adderall XR treatment period and up to 24 hours postdose in during the Adderall and MAS treatment periods. The maximum mean changes from Baseline in systolic BP were seen at 2 hours postdose during the Adderall XR (+15.7mmHg) and Adderall (+18.8mmHg) treatment periods and one hour postdose during the MAS (+16.2mmHg) treatment period.

Mean diastolic BP increased relative to Baseline at all postdose time points during the Adderall XR treatment period and up to 24 hours postdose during the Adderall and MAS treatment periods. The maximum mean changes from Baseline in diastolic BP were seen at 4 hours postdose during the Adderall XR (+9.1mmHg) treatment period and at 2 hours postdose during the Adderall (+9.1mmHg) and MAS (+10.5mmHg) treatment periods.

There was an increase in mean HR relative to Baseline at most postdose time points during the Adderall XR, Adderall, and MAS treatment periods. The maximum mean changes from Baseline in HR were seen at 6 hours postdose during the Adderall XR (+16.2bpm) and Adderall (+22.0bpm) treatment periods and at 11 hours postdose during the MAS (+19.3bpm) treatment period.

There were no notable differences in mean change from Baseline in respiration rate between during each Adderall XR, Adderall, and MAS treatment period.

Electrocardiogram: One subject had a transient prolongation of the QTc interval reported as an AE, however the event was considered by the Investigator as not suspected to be related to study drug. Another subject was discontinued from the study due to ECG ST-T segment abnormalities that were considered clinically significant by the Investigator upon initial review. A subsequent over-read of the ECGs for this subject by a central reader determined the ECGs to be normal.

Conclusion:

- The results from this study indicate that *d*- and *l*-amphetamine bioavailability after a dose of either Adderall XR or Adderall is comparable to the bioavailability of these enantiomers following a MAS dose.
- Adderall XR 30mg, Adderall 30mg, and MAS [5mg/mL] x 6mL were generally well tolerated when administered as a single oral dose.

Date of report: 30 November 2005

LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ADHD	Attention Deficit Hyperactivity Disorder
AE	Adverse Event
ALT	Alanine Transaminase (SGPT)
ALP	Alkaline Phosphatase
AST	Aspartate Transaminase (SGOT)
AUC	Area Under the Plasma Concentration-Time Curve
BLQ	Below Level of Quantification
AUC_{0-t}	Area under the drug concentration-time curve from time zero to the time of the last quantifiable plasma concentration
$AUC_{0-\infty}$, AUC_{0-inf}	Area under the drug concentration-time curve from time zero to infinity
BMI	Body Mass Index
BP	Blood Pressure
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CL/F	Oral Clearance
C_{max}	Maximum Observed Plasma Concentration
CII	Drug Enforcement Agency Scheduled Substances Class Two
CNS	Central Nervous System
CRF	Case Report Form
CV	Coefficient of Variation
DR	Delayed-Release
DSM-IV	Diagnostic and Statistical Manual of Mental Disorders, 4^{th} ed.
ECG	Electrocardiogram
K_3EDTA	Tripotassium Ethylenediaminetetraacetic Acid
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GGT	Gamma-Glutamyl Transferase
HCG	Human Chorionic Gonadotropin
HEENT	Head, Eyes, Ears, Nose, and Throat

HIV	Human Immunodeficiency Virus
HR	Heart Rate
ICF	Informed Consent Form
ICH	International Conference on Harmonisation
IR	Immediate-release
IRB	Institutional Review Board
IUD	Intrauterine Device
LC/MS/MS	Liquid Chromatography with Tandem Mass Spectrometry
LDH	Lactate Dehydrogenase
LS	Least Squares
MAS	Mixed Amphetamine Salts
MCH	Mean Corpuscular Hemoglobin
MCHC	Mean Corpuscular Hemoglobin Concentration
MCV	Mean Corpuscular Volume
MedDRA	Medical Dictionary for Regulatory Activities
ODD	Oppositional-Defiant Disorder
OTC	Over-the-Counter
PK	Pharmacokinetic
PI	Principal Investigator
QC	Quality Control
RBC	Red Blood Cells
RSD	Relative Standard Deviation
SAE	Serious Adverse Event
SCE	Sister Chromatid Exchange
SD	Standard Deviation
SI	Système International
$t_{½elim}$, $t_{½}$	Terminal Elimination Half-life
TEAE	Treatment-Emergent Adverse Event
t_{max}	Time of Occurrence of C_{max}
TSH	Thyroid Stimulating Hormone
Vz/F	Volume of Distribution
λ_z	Terminal Phase Elimination Rate Constant
USP	United States Pharmacopeia

WBC	White Blood Cell
WOCP	Women of Child-bearing Potential
WHODRUG	World Health Organization Drug Dictionary
Wt	Weight
XR	Extended-release

1. ETHICS

1.1 Institutional Review Board (IRB)

The study protocol and informed consent form (ICF) were approved by the Mid*lands Institutional Review Board, located at 8012 State Line Road, Leawood, KS, USA. Institutional Review Board approval was granted on 15 June 2005, prior to study initiation, in conformance with 21 Code of Federal Regulations (CFR) 50 and 21 CFR 56. A copy of the study protocol is presented in Appendix 1.1. The approval letter is on file with the Investigator and Sponsor. A sample Case Report Form (CRF) is presented in Appendix 1.2 and information about the IRB is given in Appendix 1.3.

1.2 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), the 41st (Hong Kong 1989) and the 48th (Somerset West [South Africa] 1996) World Medical Assemblies.

1.3 Subject Information and Consent

Before study initiation, all prospective subjects gave informed consent by signing the ICF after having received written information and an explanation of what the study involved before study initiation. A copy of the ICF was given to the subject. Signed and witnessed ICFs are on file with the Investigator. All consent documentation was required to be in accordance with applicable regulations and Good Clinical Practice (GCP) guidelines.

2. INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

This study was conducted by: Carlos A. Fierro, MD. Subjects were seen at PRA International Clinical Pharmacology Center, located at 16300 College Boulevard, Lenexa, KS, USA. Subjects were also confined at this facility for at least the first 24 hours after each dose of study drug. The study administrative structure appears below. A copy of the Investigator's curriculum vitae is located in Appendix 1.4.

Name and Affiliation	Title	Role
Carlos A. Fierro, MD PRA International Clinical Pharmacology Center	Principal Investigator	Responsible for Study Conduct
Raymond D. Pratt, MD Timothy Whitaker, MD Shire Development Inc.	Vice Presidents, Global Clinical Medicine	Medical Officers responsible for all clinical and safety aspects of the study
Bao-Van Tran, MS Shire Development Inc.	Senior Clinical Scientist	Sponsor's contact for management of the study
Brandi Lute PRA International	Project Director	Study management
Elizabeth Milligan Aris Clinical, Inc.	Clinical Research Associate, Contract Research Organization	Clinical monitoring of the study
Brian Payne, MT Physician's Reference Laboratory	Project Coordinator, Central Clinical Laboratory	Biochemistry, hematology, urinalysis, antibody screening, pregnancy testing, urine and alcohol screening
Donald Eades, PhD Shire Laboratories Inc.	Associate Director, Bioanalytical Laboratory	Quantification of measurement of *d*- and *l*-amphetamine
Kelli DiFrancesco eResearch Technology	Project Manager, Central ECG Laboratory	Centralized over-read of all ECGs

3. INTRODUCTION

3.1 Condition Background and Current Treatment

Attention Deficit Hyperactivity Disorder (ADHD) is a neurobehavioral syndrome characterized by developmentally inappropriate degrees of inattentiveness, impulsivity and hyperactivity. This disorder is among the most prevalent chronic health conditions presenting in school-age children[1], ranging from 1.7%[2] to 17.8%[3]. ADHD often persists into adolescence and adulthood[4],[5].

Stimulant medications have been used successfully to treat ADHD in children for many years. Amphetamine is known to be one of the most potent sympathomimetic amines for stimulating the central nervous system (CNS)[6]. Its proposed mechanism of action is via the release of biogenic amines from storage sites in nerve terminals. The release of norepinephrine from central noradrenergic neurons is postulated to mediate its alerting effect, its anorectic effect, and at least part of its locomotor-stimulating effect. The release of dopamine from dopaminergic nerve terminals is postulated to mediate other components of its locomotor-stimulating activity as well as the induction of stereotyped behavior. Amphetamines are also thought to block the reuptake of norepinephrine and dopamine into the presynaptic neuron. The CNS effects of amphetamines, including the paradoxical effect on hyperactivity, have led to their use as treatment for ADHD and for narcolepsy (characterized by hypersomnia that can occur quickly and at inappropriate times).

ADDERALL XR® is a long-acting, extended-release, single-amphetamine product designed for once daily oral dosing. It was approved in the USA for the treatment of ADHD in children aged 6 to 12 years in October 2001, adults in August 2004, and adolescents in July 2005. Adderall XR is an extended-release version of ADDERALL®, which has been available for the treatment of ADHD and narcolepsy in the USA since March 1996. Although Adderall has only been marketed since 1996, there are many years of prior post-marketing experience since it was previously marketed in the USA (since 1971) as Obetrol® for the treatment of obesity and 'minimal brain dysfunction' (a now out-dated description for ADHD) [7,8,9,10].

Adderall XR was approved by Health Canada in Canada for the treatment of ADHD in children in January 2004, withdrawn in February 2005, and subsequently reinstated in August 2005.

3.2 Product Background

The Food and Drug Administration (FDA) classifies Adderall XR as a single-entity amphetamine drug product, which combines the neutral sulfate salts of dextroamphetamine and amphetamine with the dextro- isomer of amphetamine saccharate and *d,l*-amphetamine aspartate monohydrate. Adderall XR capsules contain 2 types of drug-containing beads, immediate-release (IR) beads, which are designed to release the first half of the dose of the mixed amphetamine salts in a similar pattern to Adderall, and delayed-release (DR) beads, which are designed to release the second half of the dose of mixed amphetamine salts approximately 4 hours post ingestion. This gives a double-pulsed delivery of amphetamines,

which prolongs the release of amphetamine from Adderall XR compared to the conventional Adderall (immediate release) tablet formulation and thus allows once daily administration of Adderall XR capsules rather than twice daily for Adderall.

Adderall XR is commercially available in the USA in the following strengths: 5mg, 10mg, 15mg, 20mg, 25mg and 30mg. All approved strengths and 40mg, 50mg and 60mg capsules are available for clinical trial use. Clinical doses are expressed in terms of the salts.

3.2.1 Preclinical information

3.2.1.1 Introduction

Adderall XR and Adderall are approved drugs with extensive histories of clinical safety. Therefore, only brief overviews of the nonclinical pharmacology, toxicology and pharmacokinetics are provided in this report.

3.2.1.2 Pharmacodynamics

The behavioral manifestations of ADHD are believed to involve an interactive imbalance between dopaminergic and other neurotransmitter systems in the brain. Amphetamine is a noncatecholamine, sympathomimetic amine with cerebral stimulant activity. Its mode of therapeutic action in ADHD is not completely understood. However, there is substantial evidence that amphetamine increases the availability of biogenic amines (primarily dopamine and norepinephrine) in central nerve terminals and this may be the basis of its therapeutic actions in ADHD. Amphetamine is believed to increase the availability of dopamine and norepinephrine in the nerve terminals through multiple actions, including stimulating neurotransmitter release into the nerve terminal and inhibiting reuptake from the synapse[11,12].

Amphetamine has central and peripheral α- and β-adrenergic actions common to other indirectly acting sympathomimetic drugs. As a consequence, its secondary (general) pharmacologic actions at higher doses are predictable and include effects on the cardiovascular system (increases in systolic and diastolic blood pressure (BP), slowing of heart rate (HR), cardiac arrhythmias (large doses), depression of appetite, and hyperthermia[6].

3.2.1.3 Toxicology

In single-dose toxicity studies, the lethal dose at which 50% of the animals died in the group for amphetamine was 52 and 353mg/kg for mice (intravenous and oral, respectively), 70mg/kg for the rat (intraperitoneal), and 8.5mg/kg for the dog (intravenous). The estimated minimum lethal dose in monkeys is reported to be 5.0mg/kg (intravenous and oral). Sublethal doses caused increases in HR and respiratory rate, hyperactivity, hyperreactivity to auditory stimuli, and stereotypical behavior.

In repeat-dose toxicity studies, *d,l*-amphetamine was administered in the diet to mice and rats for up to 13-weeks. In mice, deaths occurred at doses of approximately 95mg/kg/day; no deaths occurred in rats at doses up to approximately 37mg/kg/day. Observations during the

study included dose-related reductions in body weight, hyperactivity and, in male mice, aggressive behavior. No histopathological changes attributed to amphetamine occurred at any dose in either species. *d,l*-Amphetamine was not carcinogenic in mice or rats treated for 2 years at doses of up to 30mg/kg/day in male mice, 19mg/kg/day in female mice, and 5mg/kg/day in male and female rats.

Amphetamine, in the enantiomer ratio present in Adderall, did not adversely affect fertility or early embryonic development in rats when dosed orally at up to 20mg/kg/day and had no effects on embryofetal development when orally administered to pregnant rats and rabbits during organogenesis at doses of up to 6 and 16mg/kg/day, respectively. In published studies involving intraperitoneal administration of *d*-amphetamine to pregnant mice, fetal malformations and death have been reported at doses of 50mg/kg/day or more. The relevance of these findings to clinical use of oral amphetamine is uncertain.

Amphetamine, in the enantiomer ratio present in Adderall was not mutagenic in *E. coli* and was not clastogenic in an *in vivo* mouse bone marrow micronucleus test using the oral route. In published studies, *d,l*-amphetamine has been reported to be equivocal in an Ames test, negative in *in vitro* sister chromatid exchange (SCE) and chromosomal aberration assays, and positive in an oral mouse bone marrow micronucleus test.

3.2.1.4 Pharmacokinetics

In rats and rabbits, orally administered amphetamine (in the enantiomer ratio present in Adderall) was rapidly absorbed with t_{max} occurring at 1 to 2 hours[13,14,15]. Plasma exposure was approximately proportional to dose except at high (toxicological) doses. The elimination half-life was between 2 and 3 hours in both species.

In mice, amphetamine is widely distributed to tissues and has been shown to cross the placental barrier after intraperitoneal or intravenous administration[16,17].

Amphetamine is extensively metabolized in animals[18]. Aromatic *para*-hydroxylation is a major route in the rat, but is less important in other species, including man. In rats, *in vitro* studies indicate that this reaction is catalyzed by CYP2D1 (CYP2D6 in man)[19,20]. Aliphatic hydroxylation (β-hydroxylation) of the side-chain, catalyzed by dopamine-β-hydroxylase, occurs in norepinephrine-containing neurons, a reaction that appears to be stereoselective for the *d*-enantiomer. All species appear to have the enzymatic capability to perform β-hydroxylation[18].

Oxidative deamination and subsequent metabolism of the deaminated product is quantitatively the most important pathway in the metabolism of amphetamine in most species other than the rat, including man[18]. In the rabbit, *in vitro* studies indicate involvement of CYP2C3 in this reaction[21].

Amphetamine was excreted predominantly in the urine of rats given a high intravenous dose (15mg/kg), with 24% to 26% of the dose appearing as parent drug and 32% to 40% appearing as the *p*-hydroxy metabolite[22].

d-amphetamine, *l*-amphetamine and *d,l*-amphetamine were not reversible or irreversible type inhibitors of human hepatic cytochromes P450 CYP1A2, CYP2C9, CYP2C19, CYP2D6 or CYP3A4/5 *in vitro*, and no substantive differences were apparent between the *d*- and *l*-amphetamine isomers[23].

3.2.2 Clinical information

3.2.2.1 Introduction

Adderall XR is approved in the USA for the treatment of ADHD in children, adults, and adolescents. Prior to this study, Shire had conducted ten Phase I pharmacokinetic (PK) and bioavailability studies in adult subjects and in children with ADHD with prior exposure to stimulants. These have been augmented by one Phase II efficacy, safety and PK study in pediatric patients with ADHD and eight Phase III efficacy and safety studies in patients with ADHD, three in children, two in adults, and three in adolescents. In these studies, 1574 subjects/patients, namely 100 healthy adult subjects, 23 healthy adolescents, 915 children with ADHD, 289 adolescents with ADHD, and 247 adult patients have received Adderall XR (or its test formulation) either as single or multiple doses. One-hundred thirty-nine (139) children with ADHD have received Adderall XR for >24 months, 284 for >18 months and 330 for >1 year.

3.2.2.2 Pharmacokinetics and metabolism

There have been no specific studies with Adderall XR investigating drug metabolism in man. However, the pharmacokinetics of Adderall XR has been characterized in 11 studies:

- 6 Phase I studies in adult subjects (371.404, 381.102. 381.103, 381.105, 381.108 and 381.109)
- 3 Phase I studies in children with ADHD with prior exposure to stimulants (381.104, 381.106 and 381.107)
- 1 Phase II study in pediatric patients with ADHD (381.201).
- 1 Phase I study in adolescent patients with ADHD (381.110)

Of the 11 studies, two were pilot studies to compare different formulations of Adderall XR and six were pharmacokinetic/bioavailability studies to characterize the final formulation. The pharmacokinetic profile of Adderall XR was evaluated in a total of 100 adult subjects, 60 children with ADHD with prior exposure to stimulants, 51 pediatric patients with ADHD, and 23 adolescents.

Adderall XR capsules and Adderall (immediate-release) tablets both contain *d*-amphetamine and *l*-amphetamine salts in the ratio of 3:1. The time to reach maximum plasma concentration (t_{max}) for both *d*- and *l*-amphetamine is about 7 hours for Adderall XR, about 4 hours longer than that for a single 10mg dose of Adderall (immediate release), which is consistent with the extended–release nature of Adderall XR.

A single dose of Adderall XR 20mg capsules provided comparable plasma concentration profiles of both *d*- and *l*-amphetamine to Adderall (immediate-release) 10mg two times daily administered 4 hours apart.

The mean elimination half-life ($t_{½}$) is 1 hour shorter for *d*- amphetamine and 2 hours shorter for *l*-amphetamine in children aged 6 –12 years compared to that in adults ($t_{½}$ is 10 hours for *d*-amphetamine and 13 hours for *l*-amphetamine in adults, and 9 hours and 11 hours, respectively, for children). In adolescents (<75 kg), the mean elimination half-life is 11 hours for *d*-amphetamine and approximately 13.5 hours for *l*-amphetamine. Adderall XR demonstrates linear pharmacokinetics over the dose range of 10 to 60mg. There is no unexpected accumulation at steady state.

Food does not affect the rate (C_{max}) or extent (AUC) of absorption of Adderall XR capsules, but prolongs t_{max} by 2.5 hours (from 5.2 hours at fasted state to 7.7 hours after a high-fat meal). Opening the capsule and sprinkling the contents on applesauce results in comparable rate and extent of absorption to the intact capsule taken in the fasted state.

3.2.2.3 Efficacy

A total of eight Phase II/III studies with Adderall XR have been reported in patients with ADHD. One additional Phase III study with Adderall XR (381.311) was conducted in adolescent patients with Oppositional-Defiant Disorder (ODD). Three of the nine Phase II/III studies were in pediatric patients with ADHD (381.201, 381.301, and 381.302), two were in adults (381.303 and 381.304), and three were in adolescents (381.314a, 381.314b and 381.315).

The efficacy of Adderall XR in the treatment of ADHD in children was established on the basis of two (381.201 and 381.301) controlled trials in children aged 6-12 years who met the Diagnostic and Statistical Manual of Mental Disorders, 4th ed. (DSM-IV) criteria for ADHD, along with extrapolation from the known efficacy of Adderall. Results of these trials demonstrated that a single morning dose of Adderall XR was effective and produced dose-dependent improvements in ADHD symptoms for up to 12 hours. Similarly, results from the placebo-controlled study in adults (381.303) showed that the signs and symptoms of ADHD were adequately controlled for up to 12 hours postdose using a once a day dosing schedule, with evidence to suggest that the minimum effective dose in adults is approximately 20mg. Final data from a completed but not yet reported study in pediatric patients (381.302) suggest that doses of 10mg-30mg daily continue to have a therapeutic effect after approximately two years treatment duration.

3.2.2.4 Safety

The safety of Adderall XR in patients with ADHD has been evaluated in two placebo-controlled studies (381.201 and 381.301) and one open label safety extension study (381.302) in children, one placebo-controlled study in adults (381.303), one open label safety extension study in adults (381.304), and one placebo-controlled study with an open-label safety component in adolescents (381.314a and 314b). The safety of Adderall XR in pediatric and adolescent patients with ODD has been evaluated in one placebo-controlled study

(381.311). Complete safety data from studies 381.305, 381.312 and ongoing study 381.315 have not yet been reported. Clinical safety data from 10 Phase I studies in pediatric patients and adult subjects are also available as supportive information.

Safety was assessed by recording of adverse events (AEs), laboratory tests, vital signs, medical history, physical examination and electrocardiogram (ECG). In addition Side Effect Ratings specific to stimulant treatment were collected by parents and teachers in study 381.201.

The most commonly reported AEs in children with ADHD were loss of appetite (coded as anorexia), headache, insomnia, abdominal pain, nervousness and emotional lability, all except headache being reported more frequently than with placebo in the largest placebo-controlled study. In adult patients loss of appetite, headache, insomnia and nervousness were also some of the most common AEs reported. However, the most common AE in adult patients was dry mouth, an AE not reported in children. Similar to the most common AEs in children, the most commonly reported AEs in adolescents with ADHD were loss of appetite, insomnia, abdominal pain, and weight loss.

Forty-seven (47) patients (25 pediatric patients, seven adolescent patients, 15 adult patients on Adderall XR) have reported 52 serious adverse events (SAEs) and two placebo patients reported three SAEs. One SAE was also reported in the compassionate use program. All except five were considered unrelated to Adderall XR; three pediatric patients experienced convulsions considered possibly related to Adderall XR, one adult patient had a manic depressive reaction considered related to Adderall XR and one adult patient had a drug-induced psychosis considered related to Adderall XR. There have been no deaths in clinical studies.

A total of 855 pediatric, 289 adolescents and 247 adult patients have been exposed to Adderall XR in Phase II/III studies. A further 60 pediatric patients and 23 adolescents have received single doses of Adderall XR in Phase I studies. In addition, a total of 100 healthy adult subjects have received single or multiple doses of Adderall XR or its experimental formulation in Phase I studies. Single doses of up to 40mg Adderall XR and multiple doses of 10mg-40mg once daily have been assessed in pediatric patients whilst adolescent and adult patients have received multiple doses of 20mg-60mg once daily. Of the 855 pediatric patients exposed to Adderall XR in Phase II/III studies 139 were exposed for >24 months, 284 for more than >18 months and 330 for more than 12 months. The distribution of exposure was not substantially different when the populations were analyzed by gender. Adult patients were exposed to Adderall XR for up to 24 months.

Overall Adderall XR is considered safe for the treatment of ADHD in children, adolescents and adults. These safety data also provide support for the use of Adderall XR in clinical studies in children and adolescents with ODD.

3.3 Rationale

This was an exploratory study to further assess the absorption profile of Adderall XR n healthy adults.

4. STUDY OBJECTIVES

4.1 Primary Objective

The primary objective of this study was to assess the relative bioavailability of single 30mg doses of Adderall XR capsules and Adderall tablets versus an oral solution of mixed amphetamine salts (MAS) [5mg/mL].

4.2 Secondary Objective

The secondary objective of this study was to describe the safety profile of single 30mg doses of Adderall XR capsules, Adderall tablets, and an oral solution of MAS [5mg/mL].

5. INVESTIGATIONAL PLAN

5.1 Overall Study Design and Plan

5.1.1 Description

This was a Phase I, randomized, open-label, single-dose, three-arm, three-period, six-sequence crossover study conducted at a single center in the U.S.

The study was to include approximately eighteen healthy adult volunteers (aged 18-55). Each of the subjects was to be randomly assigned to one of six dosing sequence groups, with approximately three subjects per sequence group. Each of the groups was to receive their assigned treatment (a single oral 30mg dose of Adderall XR capsules, Adderall tablets, or 6mL of an oral solution of MAS [5mg/mL] after an overnight fast during the first study treatment period and then were to be crossed over to receive the alternate treatments after an overnight fast for the subsequent study periods. The washout between the dosing of each study period was to be approximately seven days. Replacement subjects were not to be used.

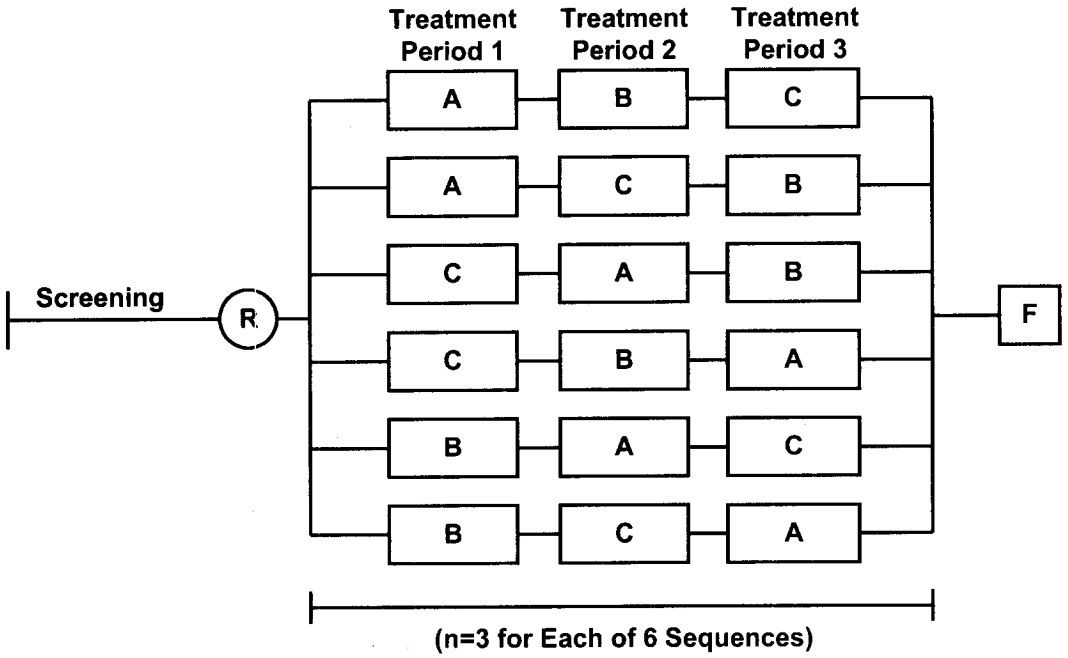
There were to be 23 blood samples collected during each study period for a total of 69 blood samples per subject for the quantification of *d*-amphetamine and *l*-amphetamine in plasma. As a result, all subjects were to have approximately 345mL of blood collected during the study (over the course of 1.5 months) for plasma analysis, 16mL for clinical laboratories, and an additional 10mL (5mL at Screening and End of Study/Withdrawal) were to be collected from women of child-bearing potential (WOCP) for pregnancy testing.

The subjects were to be confined to the clinic during each Treatment Period from approximately 12 hours prior to dosing through the 24-hour postdose assessments, and return to the clinic for 48- and 60-hour postdose assessments.

The duration of subject involvement was to be approximately 2 months.

Figure 1 is a schematic of the overall study design.

Figure 1: Study Design Flow Chart



R = Randomization
A = Adderall XR x 30mg qd
B = Adderall x 30mg qd
C = MAS [5mg/mL] x 6mL qd
F = 30-Day Follow-up Contact

5.1.2 Study schedule

The study chronology and evaluations to be performed are tabulated in the Schedule of Assessments (see Table 1 and Table 2).

Table 1: Schedule of Assessments

	Screening	Treatment Period			End of Study/ Withdrawal	Follow-up Call*
		1	2	3	3 (Day 3)	
Week	**-2 to 0**	**0**	**1**	**2**	**2 (+ 1 day)**	**6**
Informed consent/assent	✓					
Inclusion/exclusion criteria	✓	✓†	✓†	✓†		
Demographics	✓					
Medical and medication history	✓					
Physical examination	✓				✓	
Vital signs‡	✓	✓	✓	✓	✓	
Height (calibrated stadiometer)	✓					
Weight (calibrated scale)	✓	✓	✓	✓	✓	
12-lead ECG	✓	✓	✓	✓	✓	
Pregnancy Test (WOCP)§	✓	✓	✓	✓	✓	
Biochemistry and Hematology	✓				✓	
Urinalysis#	✓				✓	
Antibody Screen**	✓					
Urine Drug/Alcohol Screen	✓	✓	✓	✓		
Admission to Confinement Unit		✓	✓	✓		
Overnight Fast††		✓	✓	✓		
Standardized Meals/Snack		✓	✓	✓		
Randomization		✓				
Investigational Product Administration		✓	✓	✓		
PK Blood Draw		✓	✓	✓	✓	
Discharge from Unit		✓	✓	✓	✓	
Concomitant Medications		✓	✓	✓	✓	
Adverse Events‡‡		✓	✓	✓	✓	✓

* A visit window of 30 ± 5 days was permitted for the follow-up call week.
† A brief medical/medication interview was to be completed to confirm continued eligibility (inclusion/exclusion criteria).
‡ Included oral temperature, sitting blood pressure, heart rate, and respiratory rate. Oral temperature was only collected at Screening, Pre-dose, and End of Study/Withdrawal.
§ Serum at Screening and at the end of Treatment Period 3 (60hrs postdose) or End of Study/Withdrawal; Urine at each Check-In Period
# Microscopic examination was to be conducted if protein and/or blood were detected during urinalysis.
** Included screening for HIV antibody, Hepatitis B surface antigen, and Hepatitis C antibody.
†† All subjects were to fast for at least 10 hours prior to dosing through one hour postdose.
‡‡ Spontaneously reported AEs were to be collected after informed consent had been signed; during Screening and throughout, non-directed questioning was to occur. Ongoing AEs were to be followed to resolution, outcome, stabilization, or until otherwise explained.

Table 2: Detailed Study Day Schedule

Day	Time	Hours Post-Dose	Review of inclusion & exclusion criteria	Randomization	Physical Examination	Vital Signs*	Weight	ECG	Pregnancy Test (WOCP)†	Biochem/Hematology & Urinalysis	Urine Drug and Alcohol Screen	Admission to Confinement Unit	Std Meals/Snack	Fast‡	Investigational Prod Administration§	PK blood draw	Discharge from Unit	AE monitoring#	Concomitant medications
-1	1900	-12	✓	✓**		✓	✓	✓	✓		✓	✓	✓					✓	✓
	2200	-9												✓				✓	
1	0700	0				✓		✓						✓	✓	✓		✓	
	0715	0.25														✓		✓	
	0730	0.5												✓		✓		✓	
	0745	0.75						✓										✓	
	0800	1				✓										✓		✓	
	0830	1.5						✓								✓		✓	
	0900	2				✓										✓		✓	
	0915	2.25						✓										✓	
	0930	2.5														✓		✓	
	1000	3				✓		✓								✓		✓	
	1030	3.5														✓		✓	
	1045	3.75						✓										✓	
	1100	4				✓							✓			✓		✓	
	1130	4.5						✓								✓		✓	
	1200	5				✓										✓		✓	
	1215	5.25						✓										✓	
	1300	6				✓		✓								✓		✓	
	1400	7				✓										✓		✓	
	1430	7.5						✓										✓	
	1500	8				✓										✓		✓	
	1600	9				✓		✓					✓			✓		✓	
	1700	10				✓										✓		✓	
	1730	10.5						✓										✓	
	1800	11				✓										✓		✓	
	1900	12				✓		✓					✓			✓		✓	
	2100	14														✓		✓	
2	0700	24				✓		✓								✓	✓††	✓	
3	0700	48				✓		✓				✓	✓			✓		✓	✓
	1900	60			✓‡‡	✓	✓‡‡	✓	✓‡‡	✓‡‡			✓			✓	✓	✓	

* Included sitting blood pressure, heart rate, and respiratory rate. Oral temperature only to be collected at Screening, Pre-dose, and End of Study/Withdrawal.

† Serum at the end of Treatment Period 3 (60hr postdose) or End of Study/Withdrawal; Urine at each Check-In Period.

‡ All subjects were to fast for at least 10 hours prior to dosing through one hour postdose.

§ Administered with 8oz (240mL) water

\# Spontaneously reported AEs were to be collected after Screening and throughout; non-directed questioning was to occur. Ongoing AEs were to be followed to resolution, outcome, stabilization, or until otherwise explained.

** Conducted during Treatment Period 1 only.

†† Optional

‡‡ Conducted during Treatment Period 3 only.

5.1.3 Screening procedures: Weeks -2 to 0 (ie prior to dosing)

The Principal Investigator (PI) or his/her designee was required to obtain written informed consent and assent, where applicable, from the subject or their legally acceptable representative prior to any study related procedures being performed.

- Informed Consent/Assent
- Inclusion/Exclusion Criteria
- Demographics
- Medical and Medication History
- Physical Examination including height (using a calibrated stadiometer), and weight (using a calibrated scale)
- Sitting Vital Signs after 5 minutes of rest (oral temperature, HR, BP, and respiratory rate)
- 12-Lead ECG after 5 minutes of rest
- Hematology with complete blood count (CBC)
- Serum biochemistry
- Urinalysis and microscopic examination (if protein and/or blood were detected during urinalysis)
- Antibody screen (included screening for Human Immunodeficiency Virus (HIV) antibody, Hepatitis B surface antigen, and Hepatitis C antibody)
- Urine screen for alcohol and drugs of abuse
- Serum Pregnancy Test for all WOCP – A negative serum pregnancy test was required to be documented for inclusion into this study
- Adverse Events (any AEs occurring after Informed Consent were to be collected)
- Washout of all medications as instructed by the Investigator after subject eligibility had been confirmed, if applicable

5.1.4 Start of Confinement Period: Check-in Day –1 for All Treatment Periods (12 hours predose)

All subjects were to complete a brief written questionnaire to affirm that the eligibility criteria/restrictions had not been violated since the screening or previous confinement period.

- Check-in to the clinic (confinement facility) on evening prior to dosing
- Confirmation of continued eligibility (ie with respect to inclusion/exclusion criteria and medication history)
- Sitting Vital Signs after 5 minutes of rest (HR, BP, and respiratory rate)
- 12-Lead ECG after 5 minutes of rest

- Subject weight
- Urine alcohol and drug screen – A negative urine alcohol and drug screen was required to be documented prior to study drug dosing
- Urine Pregnancy Test for all WOCP – A negative urine pregnancy test was required to be documented prior to study drug dosing
- Commencement of fasting at least 10 hours prior to dosing (ie start between 1900 and 2100 hours)
- Standard evening meal approximately 12 hours prior to 0700 dose (optional snack at 9 hours prior to dose)
- Randomization (Treatment Period 1 only)
- Concomitant Medications
- Adverse Events (any AEs occurring after Informed Consent were to be collected)

5.1.5 Day 1 for All Treatment Periods (predose to 16 hours postdose)

- Investigational product dosing at approximately 0700 (Hour 0)
- Blood collection for plasma quantification of *d*-amphetamine and *l*-amphetamine at predose (0 hour), 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, and 14 hours postdose
- Sitting Vital Signs after 5 minutes of rest (HR, BP, and respiratory rate) at predose (0 hour), 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, and 12 hours postdose. Oral temperature at predose (0 hour) only.
- 12 Lead ECG after 5 minutes of rest at predose (0 hour), every 45 minutes for the first 6 hours, and every 1.5 hours for the next 6 hours postdose
- Standardized meals at 4 and 9 hours postdose with an optional snack at 12-14 hours postdose

5.1.6 Day 2 for All Treatment Periods (17 to 40 hours postdose)

Subjects were to remain in the confinement facility until the 24-hour postdose assessments had been completed. Subjects had the option of remaining in the confinement facility or being discharged after the 24-hour postdose assessments, but all subjects were required to return to the facility for 48- and 60-hour postdose assessments.

- Blood collection for plasma quantification of *d*-amphetamine and *l*-amphetamine at 24 hours postdose
- Sitting Vital Signs after 5 minutes of rest (HR, BP, and respiratory rate) at 24 hours postdose
- 12 Lead ECG after 5 minutes of rest at 24 hours postdose
- Adverse Events

- Discharge from confinement facility after 24 hour postdose assessments (optional)

5.1.7 Day 3 for All Treatment Periods (41 to 60 hours postdose)

Subjects who were discharged at 24 hours postdose were to return to the confinement facility for 48- and 60-hour postdose assessments. Subjects who opted to remain in the clinic overnight were to also undergo the following procedures.

- Return to the clinic at 48 hours postdose (if discharged at 24 hours postdose)
- Blood collection for plasma quantification of *d*-amphetamine and *l*-amphetamine at 48 and 60 hours postdose
- Sitting Vital Signs after 5 minutes of rest (HR, BP, and respiratory rate) at 48 and 60 hours postdose
- 12 Lead ECG after 5 minutes of rest at 48 and 60 hours postdose
- Concomitant Medications at 48 hours postdose (if discharged at 24 hours postdose)
- Adverse Events
- Discharge from confinement facility after 60 hours postdose assessments

5.1.8 Day 3 for Treatment Period 3 (41 to 60 hours postdose); End of Study/Withdrawal Procedures

The following End of Study procedures were to be completed at the end of Treatment Period 3, in addition to those listed in Section 5.1.7 above. Subjects withdrawn from the study were to complete all evaluations listed below (regardless of hour specified).

- Physical Examination at 60 hours postdose
- Subject weight at 60 hours postdose
- Hematology with CBC at 60 hours postdose
- Serum biochemistry at 60 hours postdose
- Urinalysis and microscopic examination (if protein and/or blood were detected during urinalysis) at 60 hours postdose
- Serum Pregnancy Test for all WOCP at 60 hours postdose

5.1.9 Follow-up period

A telephone contact was to occur at approximately 30 days (±5 days) post-discontinuation of investigational product to collect information on ongoing AEs and SAEs and to collect any new related AEs and any new onset SAEs. This information was to be documented in the source and the clinical and safety databases were to be updated if necessary.

5.2 Discussion of Study Design, Including the Choice of Control Groups

This study was designed to evaluate the bioavailability of single 30mg doses of Adderall XR capsules and Adderall tablets versus an oral solution of MAS [5mg/mL].

This study was a crossover design and each subject acted as his/her own control, with the comparisons being made between the PK parameters of the three treatments. A carry-over of measurable drug concentrations in plasma from one period to the next was not expected based upon the observed elimination half-life from previous PK studies.

The open-label design of this study was considered appropriate since the primary endpoints of the study were objective measurements of PK parameters.

All PK and safety measurements and assessments integrated in the design of this study are widely used and generally recognized as reliable, accurate, and relevant. Alternative measures of bioavailability were not considered.

5.3 Selection of Study Population

5.3.1 Inclusion criteria

Subjects were to meet the following criteria to be eligible to participate in the study:

1. Voluntary, documented consent to participate in this study.

2. Healthy males and females, 18 to 55 years of age, inclusive.

3. Female subjects were to be either post-menopausal (amenorrhea for at least 12 consecutive months), surgically sterile, or non-pregnant WOCP who were using or agreed to use acceptable methods of contraception. Acceptable contraceptives included intrauterine devices (IUDs), hormonal contraceptives (oral, depot, patch, injectable, or vaginal ring), and double barrier methods such as condoms or diaphragms with spermicidal gel or foam. For WOCP a serum beta-Human Chorionic Gonadotropin (HCG) pregnancy test at Screening and a urine pregnancy test at Check-in Day -1 of each Treatment Period must have been conducted. The result was required to be negative at Screening and at all Check-in periods. WOCP were to be advised to use acceptable contraceptives throughout the study period and for 30 days after the last dose of investigational product. If hormonal contraceptives were used, they were to be taken according to the package insert. Women of childbearing potential who were not currently sexually active at the time of entering the study were required to agree to use acceptable contraception, as defined above, if they decided to become sexually active during the period of the study and for 30 days after the last dose of investigational product.

4. No clinically significant abnormal findings on the physical examination, medical history, ECG, or clinical laboratory results during Screening or at Check-in. The Phase I unit was to request full medical histories from the subject's primary physician prior to enrollment into the study, if the subject had a primary physician and if the subject agreed to the

primary physician being informed of the subject's participation in the study. The request and the primary physician's response were to be documented in the source.

5. Body Mass Index between 20kg/m^2 and 29kg/m^2.

6. Must understand and be able, willing and likely to fully comply with study procedures and restrictions.

5.3.2 Exclusion criteria

Subjects were not to participate in the study if any of the following conditions existed at Screening and/or Check-in for Treatment Period 1:

1. Current or recurrent disease that could affect the action, absorption or disposition of the investigational product, or clinical or laboratory assessments.
2. Current or relevant previous history of serious, severe or unstable (acute or progressive) physical or psychiatric illness, any medical disorder that may have required treatment or made the subject unlikely to fully complete the study, or any condition that would present undue risk from the investigational product or procedures.
3. History of gastrointestinal, renal, hepatic, endocrine, oncologic, hematologic, neurologic, psychologic, immunologic, or pulmonary disorders, or cardiovascular disease; or a history of tuberculosis, epilepsy, diabetes, psychosis, glaucoma, 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 or prevent the subject from completing all arms of the study.
4. Any history of uncontrolled hypertension.
5. Baseline BP reading of >139/89mmHg.
6. Subjects with a known or suspected structural cardiac abnormality by history or physical examination.
7. Any history of seizure (other than infantile febrile seizures), a tic disorder, a current diagnosis and/or family history of Tourette's Disorder.
8. Any clinically significant laboratory abnormalities at Screening, in the opinion of the Physician Investigator.
9. Use of any prescription medication (requiring more than a 7-day washout) within 7 days prior to Check-in Day –1, Treatment Period 1, excluding hormonal contraceptive or hormone replacement therapy.
10. Use of any over-the-counter (OTC) medication within 7 days of Day -1.
11. Treatment with any known enzyme-altering agents (barbiturates, phenothiazines, cimetidine, etc) within 30 days prior to Day -1 or during the study.
12. Known or suspected intolerance or hypersensitivity to amphetamine, Adderall XR, Adderall, or any related drug.
13. Any history of alcohol or other substance abuse.

14. Use of tobacco in any form (eg smoking or chewing) or other nicotine-containing products in any form.
15. Positive urine screen for drugs of abuse.
16. Use of another investigational product or participation in a clinical trial within the last 30 days prior to enrollment.
17. Donation of blood or plasma (500mL or more) within 56 days prior to enrollment.
18. Female subjects who were pregnant or lactating, including females with a positive pregnancy test at Screening or Check-in of any period were to be excluded.
19. Subjects that had previously been enrolled into this study and subsequently withdrawn were to be excluded.
20. Abnormal diet or substantial changes in eating habits within 30 days prior to Day –1 of the first treatment period, as assessed by the Investigator.

5.3.3 Subject restrictions

Subjects were to be restricted from having foods or beverages containing alcohol or caffeine/xanthine 48 hours prior to each period of confinement through 60 hours postdose. Subjects were not to consume fruit, juices, or foods containing ascorbic acid during the periods of confinement. The use of concomitant medications during the course of the study was prohibited. The use of any prescription medication or OTC medication (requiring more than a 7-day washout) within 7 days prior to Check-in (excluding hormonal contraceptives or hormone replacement therapy) was prohibited.

If the subject required any concomitant medications during participation in the study, the medications were to be documented, and the subject's continued participation was to be assessed by the Investigator at the next visit. If the Investigator determined that the subject was to be withdrawn from the study, the reason for withdrawal was to be recorded in the source and in the CRF.

5.3.4 Removal of subjects from therapy or assessments

Subjects were free to withdraw from the study at any time for any reason without prejudice to his/her future medical care by the physician or at the institution. The Investigator or Sponsor may have also withdrawn the subject at any time in the interest of subject safety or study integrity. The primary reason for withdrawal was to be recorded in the subject's medical record and on the withdrawal form in the CRF. If a subject was withdrawn for more than one reason, each reason should have been documented in the source document, and the most medically significant reason should have been entered on the CRF.

The withdrawal of a subject from the study was to be discussed, where possible, with the Medical Monitor and/or Clinical Manager before the subject stopped investigational product. If investigational product was discontinued, the final evaluations were to be performed as completely as possible. Subjects who discontinued were not to be replaced. Any comments (spontaneous or elicited) or complaints made by the subject and the reason for termination, date of stopping the investigational product, and the total amount of investigational product taken was to recorded in the CRF and source documents.

Potential reasons for withdrawal included:

- Consent was withdrawn or the subject refused to continue treatment and/or procedures/observations
- The clinical condition under study required alternative treatment
- Occurrence of unmanageable AEs or if the subject required concomitant medication disallowed under this protocol)
- The subject became pregnant
- Other reasons (eg significant protocol violation, non-compliance).

At least three documented attempts were to be made to contact any subject lost to follow-up, one of which was to include sending a certified letter to the subject's last known address, requesting that they return to the study site for final safety evaluations.

5.4 Study Treatments

5.4.1 Description and batch information of investigational product(s)

Subjects received a single dose of each of the following (order based on randomized assignment); 30mg capsule of Adderall XR, 30mg tablet of Adderall, or 6mL of an oral solution of MAS [5mg/mL] (depending on randomization schedule) at approximately 0700 (Hour 0). Capsules and tablets were to be taken whole with 8 ounces of water. Table 3 provides a description and batch number information of the investigational products used in this study.

Table 3: Description and Batch/Lot Number Information of Investigational Products

Study Drug	Dose	Batch/Lot #
Adderall XR	1x30mg capsule	A07566A
Adderall	1x30mg tablet	A07494A
MAS [5mg/mL]	1X6mL oral solution	Amphetamine Sulfate, United States Pharmacopeia (USP) CII=A10753 Dextroamphetamine Sulfate, USP CII=A12184 Amphetamine Aspartate, CII=A11900 Dextroamphetamine Saccharate, CII=A12339

Shire provided unconstituted powdered MAS [5mg/mL] in high density polyethylene vials to be reconstituted in Sorbitol, USP 70% by the site pharmacist. All investigational product provided by Shire was labelled with a minimum of the protocol number, pharmaceutical dosage form (including product name and quantity in bottle), directions for use, storage

conditions, expiry date (if applicable), batch number or packing reference, the statements 'For clinical trial use only', and/or 'CAUTION: New Drug - Limited by Federal (United States) Law to Investigational Use', and 'Keep out of reach of children', and the Sponsor's name and address.

The site pharmacy purchased commercially available Adderall XR and Adderall.

5.4.2 Method of assigning subjects to treatment groups

The actual treatment given to individual subjects was determined by a block-randomization schedule prepared by PRA International (Appendix 1.7). The randomization schedule was based on a pair of orthogonal Latin squares for three treatments randomizing a total of 18 subjects, with three subjects randomized to each of the six treatment sequences. The randomization schedule was produced by computer software that incorporates a standard procedure for generating random numbers.

5.4.2.1 Allocation of subjects to treatment

Three-digit subject identifiers were to be allocated as all subjects consented to take part in the study. Within the investigational site, this number was to be allocated to subjects according to the sequence of presentation for trial participation.

The randomization number used in this study consisted of four-digits, starting from 1001. Once eligibility had been confirmed, subjects were to be sequentially allocated to the next unallocated randomization number in the sequence during Check-In Day –1 of Treatment Period 1. Randomized subjects were to receive the treatment conditions in the order that corresponds to the treatment sequence associated with that randomization number. Once a unique subject identifier or randomization number had been assigned, no attempt was to be made to use that number again if, for example, a subject was withdrawn from the study. If a randomization number was allocated incorrectly, no attempt was to be made to remedy the error once the investigational product had been dispensed. The subject was to continue with the allocated number and investigational product or treatment sequence, and the Clinical Manager was to be notified as soon as the error was discovered. Admission of subsequent subjects was to continue using the next unallocated number in the original numbering sequence.

5.4.3 Selection of doses in the study

The 30mg capsule of Adderall XR and the 30mg tablet of Adderall are the highest commercially available dosages of these products. The administration of 6mL of a 5mg/mL solution of MAS was chosen to match the dosage of the Adderall XR and Adderall.

5.4.4 Selection and timing of dose for each subject

Subjects were to receive a 30mg capsule of Adderall XR, a 30mg tablet of Adderall, or 6mL of an oral solution of MAS [5mg/mL] administered using an oral syringe on the dosing day, depending on the subject's randomized treatment schedule.

Under direction of designated study personnel, each dose of Adderall XR, Adderall, or MAS solution was to be administered at Hour 0 (approximately 0700) after an overnight fast of not less than 10 hours. Each dose was to be administered with 8 fluid ounces (240mL) of room temperature tap water. Subjects were to swallow the capsule or tablet intact. A mouth check was to be performed after dosing.

Subjects were not to be permitted to lie down for the first four hours following administration of the drug to assure proper physiologic stomach emptying.

5.4.5 Meal schedule

All subjects were to fast for at least 10 hours prior to dosing. A standard clinic evening meal was to be provided (approximately 12 hours prior to dose administration). Water was to be allowed *ad lib* during the study, except for 1 hour prior through 1 hour postdose.

All subjects were to continue to fast through 4 hours following drug administration, at which time a standard clinic menu and meal schedule was to be followed. The hours listed are approximate in relation to time of dosing:

Hour 0 (Dose time):	Approximately 0700
Lunch:	4-5 hours postdose
Dinner:	9-10 hours postdose
Evening snack:	12-14 hours postdose

Subjects were able to eat at any time after the completion of Day 1 (ie start of Day 2). An optional lunch was to be provided for all subjects on Day 3 of each Treatment Period, when subjects returned to the clinic for the 48- and 60-hour postdose assessments.

The same menu and meal schedule was to be administered uniformly for all subjects at each treatment period. Each subject was to eat all of the food given.

5.4.6 Blinding

This was an open-label, crossover study. The primary endpoints of this study were objective measurements of PK parameters. The study drug treatments were clearly labelled and identifiable. Therefore, blinding of the subjects, Investigator, or Sponsor was not required.

5.4.7 Prior and concomitant therapy

There were to be no serious concomitant illnesses at the time of entry into the study. Illnesses first occurring or detected during the study were to be documented as AEs in the

source document and CRF. The use of any prescription medication or OTC medication (requiring more than a 7 day washout) within 7 days prior to Check-in (excluding hormonal contraceptives or hormone replacement therapy) was to be prohibited.

If the subject required any concomitant medications during participation in the study, the medications were to be documented and the subject's continued participation was to be assessed by the Investigator at the next visit. If the Investigator determined that the subject had to be withdrawn from the study, the reason for withdrawal was to be recorded in the source and in the CRF.

5.4.8 Treatment compliance

Study center personnel administered each dose of study drug. The time of dose administration was to be recorded in the CRF.

To ensure that each dose was taken, study personnel were to perform a mouth check after drug administration.

5.5 Study Assessments

5.5.1 Pharmacokinetic assessments

5.5.1.1 Sampling schedule

During each treatment period, venous blood samples for bioanalytical analysis of *d*- and *l*-amphetamine were to be collected from the antecubital vein via direct venipuncture or indwelling catheter into a Vacutainer® tube containing tripotassium ethylenediaminetetraacetic acid (K_3EDTA) as the anticoagulant. Blood samples for bioanalytical analysis of *d*- and *l*-amphetamine were to be collected prior to dosing and at 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 3.5, 4, 4.5, 5, 6, 7, 8, 9, 10, 11, 12, 14, 24, 48, and 60 hours following dose administration.

5.5.1.2 Methodology, storage and shipment

Immediately after each collection, the K_3EDTA Vacutainer® tube was to be centrifuged at 4°C, 3000 rpm, for 10 minutes. The separated plasma was to be divided into two transfer tubes (1 to 1.5mL of plasma in primary tube and in back-up tube) labelled with the study number, visit number, subject number, collection date, and time point. All plasma samples were to be stored at -70°C or colder prior to shipment for analysis.

Pharmacokinetic samples were to be shipped to Shire Laboratories Inc., Rockville, MD for quantification of *d*- and *l*-amphetamine; on dry ice in an insulated container according to regulations. The primary and back-up samples were to be shipped at separate times.

5.5.1.3 Bioanalytical assay

A validated liquid chromatography with tandem mass spectrometry (LC/MS/MS) method was used to determine *d*- and *l*-amphetamine concentrations for each sample. Complete details of the assay method and calculation method are provided in Appendix 3.

5.5.1.4 Summary of assay performance

The validated LC/MS/MS quantification of *d*-amphetamine and *l*-amphetamine had a quantitation range of 0.5ng/mL to 75.0ng/mL using 0.5mL plasma. Deuterated racemic amphetamine (50µL; 800ng/mL) was used as the internal standard for all calibration and quality control samples. The mean correlation coefficient for the calibration curve was greater than 0.9995.

The mean concentration statistics for both *d*-amphetamine and *l*-amphetamine calibration standards are presented in Table 4. The mean percent accuracies, excluding outliers, ranged from 94.2% to 113.4% of the target concentrations, and the precision ranged from 0.9% to 2.9% for both the enantiomers. The mean percent accuracies of both *d*- and *l*-amphetamine quality control (QC) samples, as presented in Table 5, ranged from 93.9% to 99.1% and the precision ranged from 1.6% to 2.9%.

Table 4: Calibration Standard Statistics for *d- and l*-Amphetamine

Standard Concentration (ng/mL)	0.50	1.00	2.00	5.00	15.00	25.00	50.00	75.00
d-Amphetamine								
N	19	19	19	19	19	19	19	19
Mean (ng/mL)	0.6	1.0	1.9	4.7	14.5	25.0	50.4	75.4
SD	0.02	0.02	0.04	0.10	0.26	0.32	0.69	0.87
%RSD	2.9	2.3	1.9	2.2	1.8	1.3	1.4	1.1
%Accuracy	113.4	99.3	95.0	94.2	96.9	99.9	100.8	100.6
l-Amphetamine								
N	18	19	19	19	19	19	19	19
Mean (ng/mL)	0.6	1.0	1.9	4.8	14.6	25.0	50.3	75.4
SD	0.01	0.02	0.03	0.08	0.25	0.32	0.61	0.68
%RSD	2.2	2.5	1.8	1.7	1.7	1.3	1.2	0.9
%Accuracy	112.2	99.5	95.1	95.3	97.5	100.0	100.6	100.5

Source: Appendix 3.1, Bioanalytical Report Section 7, Tables 5 and 6
SD=Standard deviation
%RSD=Relative Standard Deviation

Table 5: Quality Control Sample Statistics for *d- and l*-Amphetamine

QC Concentration	Low (1.5ng/mL)	Medium (20ng/mL)	High (60ng/mL)
d-Amphetamine			
N	38	37	38
Mean (ng/mL)	1.4	19.4	59.5
SD	0.03	0.32	1.51
%RSD	2.5	1.7	2.5
%Accuracy	93.9	96.9	99.1
l-Amphetamine			
N	38	37	38
Mean (ng/mL)	1.4	19.4	59.3
SD	0.04	0.31	1.51
%RSD	2.9	1.6	2.6
%Accuracy	94.4	97.1	98.8

Source: Appendix 3.1, Bioanalytical Report Section 7, Table 7 and 8
SD=Standard deviation
%RSD=Relative Standard Deviation

5.5.2 Safety assessments

5.5.2.1 Adverse events

An AE was any untoward medical occurrence in a clinical investigation subject administered a pharmaceutical product and which did not necessarily have a causal relationship with this treatment. An AE could therefore have been any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, disease or exacerbation of a pre-existing condition temporally associated with the use of a medicinal (investigational) product[24].

All AEs were to be recorded from the time the informed consent was signed until the Follow-up telephone contact had occurred and were to be recorded on the appropriate AE pages in the CRF and/or in source documents. Where possible, a diagnosis rather than a list of symptoms was to be recorded. If a diagnosis had not been made then each symptom was to be listed individually.

Furthermore, from the post-study visit until 30 days following the last exposure to the investigational product, new related AEs and new onset SAEs were to be recorded. This information was to be collected during the 30-day Follow-up telephone contact.

It was the Principal Investigator's responsibility to review the results of all diagnostic procedures and laboratory tests as they became available. If any diagnostic procedures or

laboratory tests were performed for the study or if additional procedures or tests were done as a part of the subject's care, it was the Investigator's responsibility to ascertain whether there was a clinically significant change from Baseline for that individual subject. If the results were determined to be a clinically significant change from Baseline for that subject, this was to be defined as an AE. (This determination, however, did not necessarily need to be made the first time an abnormal value was observed. The Investigator could repeat the diagnostic procedure or laboratory test or request additional tests to verify the results of the original tests.) When possible, a diagnosis associated with the abnormality was recorded.

The Investigator was to review each AE and make the determination of relationship to study drug. The Investigator was to decide whether, in his or her medical judgement, there was a reasonable possibility that the event may have been caused by the investigational product. If no valid reason existed for suggesting a relationship, then the AE was to be classified as 'not suspected'. Otherwise, if there was any valid reason, even if undetermined or untested, for suspecting a possible cause-and-effect relationship between the investigational product and the occurrence of the AE, then the AE should have been considered 'suspected'.

The medical assessment of intensity was to be determined by using the following definitions:

a) Mild – The AE is easily tolerated and does not interfere with usual activity.

b) Moderate – The AE interferes with daily activity, but the subject is still able to function.

c) Severe – The AE is incapacitating and the subject is unable to work or to complete usual daily activities.

In general, changes in intensity during the course of an AE or worsening of pre-treatment events after initiation of investigational product were to be recorded as new AEs.

Serious AEs (as defined by the FDA CFR, Chapter 1, part 312.32), 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.

AE outcomes may have been classified as resolved, unresolved, resolving, resolved with sequelae, fatal or unknown.

5.5.2.2 Laboratory parameters

All laboratory assays were performed by Physician's Reference Laboratory according to Physician's Reference Laboratory's normal procedures. Reference ranges were supplied by Physician's Reference Laboratory and used to assess the laboratory data for clinical significance and out of range pathological changes. Abnormal laboratory values that were unexpected or not explained by the subject's clinical condition were to be repeated until confirmed, explained, or resolved.

The following laboratory assessments were to be performed:

Biochemistry

Blood samples (4mL) for biochemistry were to be taken at the Screening visit and the End of Study/Withdrawal visit. The following parameters were to be assessed:

Cholesterol	Aspartate Transaminase (AST)
Phosphorus	Alanine Transaminase (ALT)
Sodium	Alkaline Phosphatase (ALP)
Potassium	Gamma glutamyl transferase (GGT)
Calcium	Uric Acid
Urea Nitrogen	Total bilirubin
Creatinine	Glucose
Albumin	Lactate Dehydrogenase (LDH)
Total protein	Thyroid Stimulating Hormone (TSH)

Changes from Screening were to be recorded as an AE if clinically significant.

Hematology

Blood samples (4mL) for hematology were to be taken at the Screening visit and the End of Study/Withdrawal visit. The following parameters were to be assessed:

Hemoglobin	Mean corpuscular volume (MCV)
Hematocrit	Mean corpuscular hemoglobin (MCH)
Red blood cells (RBC)	Mean corpuscular hemoglobin concentration (MCHC)
Platelet count	White blood cell count – total and differential (WBC)
Bands	Neutrophils
Monocytes	Eosinophils
Lymphocytes	Basophils

Blood samples were also to be screened for the HIV antibody, Hepatitis B surface antigen, and Hepatitis C antibody at Screening.

Changes from Screening were to be recorded as an AE if clinically significant.

Urinalysis:

Urine samples (10mL) were to be collected for urinalysis at the Screening visit and the End of Study/Withdrawal visit. The following parameters were to be assessed:

Specific gravity	Ketones
PH	Blood
Protein	Bilirubin
Glucose	

If protein and/or blood were detected during urinalysis, microscopic examination was to be conducted. The microscopic examination was to consist of RBC, WBC, casts, and bacteria.

Changes from Screening were to be recorded as an AE if clinically significant.

A urine drug (cannabinoids, amphetamines, opiates, and cocaine) and alcohol screen were to be conducted at the Screening visit and at each Check-in.

5.5.2.3 Physical examination

A full physical examination including weight was to be performed at the Screening and End of Study/Withdrawal visits by a qualified individual, licensed in his/her respective state, who is either a physician, Physician Assistant, or a Nurse Practitioner. Height was to be measured at Screening. A review of body systems was to include the following:

- General appearance
- Skin
- HEENT (Head, Ears, Eyes, Nose, Throat)
- Spine/Neck/Thyroid
- Respiratory
- Cardiovascular
- Abdomen (including liver and kidneys)
- Nervous System
- Musculoskeletal
- Neurological

Any abnormalities or changes in intensity noted during the review of body systems were to be documented in the medical record and reported as an AE. In addition, resolutions of any abnormal findings during the study were to be noted in medical record and/or the CRF if clinically significant.

5.5.2.4 Vital signs

Measurements of vital signs (systolic and diastolic BP), HR, and sitting respiratory rate) were to be performed at all study visits. Blood pressure, HR, and respiratory rate were to be determined after the subject had been in the sitting position for 5 minutes.

Blood pressure was to be determined by cuff (manual or automated was acceptable although the same method and the same arm was to be used throughout the study and, where feasible, should have been taken by the same person). A BP cuff appropriate for the subject's arm length and girth was to be used for all BP measurements. The cuff was to be approximately 2/3 the length/width of the subject's arm (from elbow to shoulder). Any clinically significant deviations from vital signs at Screening were to be recorded as an AE.

Oral temperature was only to be collected at Screening, Pre-dose for each treatment period, and End of Study/Withdrawal.

5.5.2.5 Electrocardiogram

Twelve-lead ECGs were to be performed at all study visits. Electrocardiograms were to be taken at predose (0 hour), every 45 minutes for the first 6 hours, every 1.5 hours for the next 6 hours, and at 24, 48, and 60 hours postdose. Subjects were to be assessed in a quiet state (after five minutes of rest) in the supine position. A standard ECG recording device was to be utilized with the standard paper rate of 25mm/second and the standard scale setting of 10mm/mvolt.

Subjects were not eligible for inclusion in this study if they had an abnormal ECG at Screening (see Appendix 2 of the study protocol, Appendix 1.1).

The centralized ECG reader, eResearch Technology, evaluated all ECGs according to eResearch Technology's normal procedures. Reference ranges were supplied by eResearch Technology and used to assess the ECG data for abnormal and out of range readings. Abnormal ECG readings that were unexpected or not explained by the subject's clinical condition were to be repeated until confirmed, explained, or resolved. Abnormal ECGs deemed to be clinically significant by the Investigator or Sub-Investigator (who was a licensed medical doctor) were to be recorded as AEs.

5.5.2.6 Pregnancy testing

A serum beta-HCG pregnancy test (requiring 5mL of blood) was to be performed on all WOCP at the Screening visit and End of Study/Withdrawal. A urine pregnancy test was to be administered at each Check-in period. Entry into each study period was contingent upon a negative result.

5.5.2.7 Other safety assessments

A complete medical history, including a medication history, was to be performed by the Investigator at Screening. The Phase I unit was to request full medical histories from the

subject's primary physician prior to enrollment into the study, if the subject had a primary physician and if the subject agreed to the primary physician being informed of the subject's participation in the study. The request and the primary physician's response were to be documented in the source.

The history was to include but was not limited to:

- Age
- Gender
- Race
- Recent ingestion of medication (during the one month prior to Screening)
- History of respiratory, cardiovascular, renal, gastrointestinal, hepatic, endocrine, hematological, neurological, psychiatric, and other diseases

Height was to be measured at Screening. Body weight was to be measured at each visit, including Screening, each Check-in, and End of Study/Withdrawal. A calibrated stadiometer was to be used for all height measurements. For weight, the same calibrated scale was to be used at each visit, and the subject was to be instructed to remove clothing and shoes and wear a gown to ensure consistency between measurements. All measurements should have been performed by the same site personnel (if possible) throughout the study.

5.5.3 Appropriateness of measurements

All PK and safety measurements and assessments are widely used and generally recognized as reliable, accurate, and relevant.

5.6 Data Quality Assurance

This study was sponsored by Shire Development Inc. and conducted at PRA International's Clinical Pharmacology Center according to the International Conference on Harmonisation (ICH) GCP. Representatives from Aris Clinical Inc. were responsible for monitoring the study.

The following steps, visits and procedures were carried out to ensure accurate, consistent and complete data and to assure quality:

- A prestudy site visit was made to confirm the adequacy of the site and associated study personnel
- A study initiation meeting was arranged for the site to review the protocol, CRF, and procedural requirements with the Investigators and other study personnel
- A central laboratory was used for analysis of laboratory data and ECG data to ensure consistent analysis of specimens, permit uniform reporting, and minimize variability.
- CRF was used to permit consistent collection of data

PRA International's Clinical Pharmacology Center was responsible for the conduct of this trial and accuracy of all collected data. The Investigator and staff at the PRA International Clinical Pharmacology Center are well trained in conducting clinical trials. Protocol specifications and a detailed time and events schedule were prepared by the PRA International Clinical Pharmacology Center to assure consistent execution of the protocol throughout the study. The PRA International Clinical Pharmacology Center 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. The study monitor from Aris Clinical Inc. visited the PRA International Clinical Pharmacology Center to monitor the study progress and/or study documents.

5.6.1 Monitoring and auditing

Visits to the investigative site were conducted by representatives of Aris Clinical Inc. to inspect study data, patients' medical records and CRFs in accordance with current GCP and the respective local and national government regulations and guidelines. Source data reviewed during this study included, but was not limited to: subject's medical file, original laboratory reports, and ECG reports.

5.6.2 Data management

PRA International assumed the following responsibilities with approval from the sponsor: creating the CRF, database design and validation; CRF tracking; data entry; creation of data management plan; edit check specification, and programming of computerized edit checks; and coding of medical history, AEs, and concomitant medications.

Pharmaceutical Research Associates Clinical Data Manager version 2.0 was employed for data entry, management, and the majority of data quality checks. Additional checks and data review listings were developed with SAS® version 8.2 software. Medical history, AEs, and concomitant medications were coded using Medical Dictionary for Regulatory Activities (MedDRA), version 8.0 and World Health Organization Drug Dictionary (WHODRUG), version 1st Quarter 2005, respectively.

The electronic data included all PK and ECG data. Data from CRFs were double-key entered into the PRA Clinical Data Manager electronic database. Data were reviewed using both computer edit checks and manual review. The study specific Data Management Plan outlined the programmatic and manual validation checks to be performed on the collected data. Items that deviated from the specifications were sent to the Investigator for review and clarification via data clarification forms.

After all CRF data were entered, verified, and validated, and all queries were received and resolved, a final QC review of the CRFs was performed. Procedures for final QC review of the completed and closed subjects were performed as outlined in the Data Management Plan.

The clinical database was locked on 12 September 2005. Subsequently, at the study site closeout visit on 13 September 2005, the study monitor found an uncollected CRF page. The CRF page was an unscheduled vital sign page, numbered "Page 19.1" for Subject 1-410. As

this was not a scheduled CRF page, it was not identified on a missing CRF pages report that was generated prior to database lock. A decision was made by the Sponsor to not unlock the database for entry of these data on the missing CRF page. This decision was based on the assumptions that 1) this was not a blinded study, but rather an open-label PK study with well-characterized marketed products, and 2) the overall safety results and analyses were not affected by these missing data. A note to file was generated and can be found in the Trial Master File. A detailed discussion of the missing vital sign values can be found in Section 8.5.2.

5.7 Data Analyses

5.7.1 Statistical analysis plan

The following sections describe statistical methods outlined in the study protocol (Appendix 1.1) and in the final statistical analysis plan dated 12 August 2005 (Appendix 1.9).

5.7.1.1 Study populations

Safety population

The safety population was defined as all randomized subjects who received at least one dose of a study medication. This population was used for most study conduct and safety analyses.

Pharmacokinetic population

The PK population was defined as all safety population subjects who had sufficient postdose blood samples in at least one study period to estimate both the C_{max} and area under the plasma concentration-time curve (AUC) PK parameters. This population was used for all PK-related analyses.

5.7.1.2 Analysis variables

Primary outcome: Pharmacokinetic variables

The primary outcome measures in this Phase 1 study were comprised of PK parameters calculated from plasma concentrations of *d*- and *l*-amphetamine by non-compartmental techniques using WinNonlin® Professional version 4.1 or higher[25]. All calculations were based on actual sampling times. Calculated PK parameters included the following:

C_{max} Maximum observed plasma concentration

AUC_{0-t}	Area under the plasma concentration-time curve from time zero to the time of the last postdose quantifiable plasma concentration obtained by the linear trapezoidal method. A minimum of four concentrations were required for calculation of this parameter. Otherwise, it was considered to be missing
$AUC_{0-\infty}$	Area under the plasma concentration-time curve for the 0 infinity interval, calculated as $AUC_{0-t} + C_{last}/\lambda_z$, where C_{last} was the last quantifiable plasma concentration and λ_z is the terminal phase elimination rate constant, determined from the negative of the slope of the regression of log concentration on time in a terminal linear phase of three or more time points. If the C_{last}/λ_z component is greater than 30% of $AUC_{0-\infty}$ then $AUC_{0-\infty}$ was considered to be missing
t_{max}	Time of occurrence of C_{max}
$t_{1/2elim}$	Terminal elimination half-life, calculated as $\ln(2)/\lambda_z$
CL/F	Apparent oral clearance, calculated as drug dose divided by $AUC_{0-\infty}$
CL/F/Weight (Wt)	CL/F divided by subject weight in kg
V_z/F	Volume of distribution, calculated as drug dose divided by $[\lambda_z \times AUC_{0-\infty}]$
$V_z/F/Wt$	Vz/F divided by subject weight in kg

Secondary outcomes: Safety variables

Safety measures were to include the collection of AEs, clinical laboratories, vital signs (systolic and diastolic BP, HR, and sitting respiratory rate), ECGs, physical examinations, and weight.

5.7.1.3 Determination of sample size

The primary PK parameters for this study were $AUC_{0-\infty}$ and C_{max}. It was expected that the estimated $AUC_{0-\infty}$ test-to-reference ratio would be within the range of 0.90 to 1.10. Results from previous studies with various comparisons of Adderall XR capsule strength formulations (studies SLI381-104, -106, -107, -109, and -110) showed that the within-subject-between-formulation standard deviation (SD) on the natural log scale ranged from 0.054 to 0.112 for $AUC_{0-\infty}$ and 0.09 to 0.181 for C_{max}. Since the emphasis in this study was placed on $AUC_{0-\infty}$, the SD used to estimate the sample size was 0.145 (the approximate average of the maximums 0.112 and 0.181). Given that the true $AUC_{0-\infty}$ mean ratio of test to reference would be within the range of 0.90 to 1.10, the proposed crossover design would have 80% power to reject the null-hypothesis of bioequivalence at the 0.05 level of significance with a sample size of 18 subjects.

5.7.1.4 Statistical methods

The software used for all summary statistics and statistical analyses was SAS® Version 8.2.

General continuous data were summarized with the following descriptive statistics: number of observations, mean, SD, median, minimum, and maximum. Pharmacokinetic concentration and parameter summaries also included the CV and in selected cases the geometric mean (for C_{max} and AUCs). Categorical data were summarized with frequencies and percentages.

Missing or invalid data were treated as missing, not imputed.

Any statistical tests conducted were two-sided tests at a significance level of 0.05.

All study data were included in study data listings.

Pharmacokinetic analyses

Plasma Concentrations

Descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) were used to summarize the plasma concentrations of *d*- and *l*-amphetamine at each time of measurement. For purposes of descriptive summary, plasma concentrations below level of quantification (BLQ) were set to zero.

A mixed model analysis of variance of the natural log-transformed concentrations using SAS® PROC MIXED with a random term for subject-within-sequence and fixed terms for sequence, period, and treatment was used to provide p-values for pair-wise treatment comparisons of the concentrations at each time of measurement.

Linear and semi-logarithmic plots of the mean and individual plasma concentration-by-scheduled-sampling-time of *d*- and *l*-amphetamine were provided.

All individual subject plasma concentration data were listed as recorded (that is, with BLQs).

Pharmacokinetic parameters

For estimation of PK parameters, concentrations that were below level of quantification (BLQ) were assigned a value of zero if they preceded quantifiable samples in the initial portion of the profile. A BLQ that occurred at the end of the profile, or was embedded between two quantifiable points, was assigned a value of missing. If consecutive BLQs in the terminal portion of the profile were followed by quantifiable determinations, these quantified values were excluded from PK analysis by assigning them a value of missing. Plasma concentrations used to determine PK parameters were listed.

All available *d*- and *l*-amphetamine plasma concentration data from subjects were evaluated for PK unless the data were impacted by a significant protocol deviation. Changes to procedures which may have impacted the quality of the PK data were considered significant protocol deviations. These changes included any circumstances that altered the evaluation of the PK, for example, vomiting immediately following oral dosing, sample processing errors that led to inaccurate bioanalytical results, and/or inaccurate dosing on the day of the PK

sampling. In the case of a significant protocol deviation, PK data collected during treatment periods were excluded from the study results.

Other changes to the procedures that did not impact the quality of the PK data were not considered significant protocol deviations. If such changes occurred, data were included, but the analysis was adjusted accordingly. A common example of a non-significant protocol deviation was a missed blood sample or a deviation from scheduled blood collection times. Although these changes were non-significant, they were deviations from the protocol and were documented.

For each PK population subject, PK parameters were calculated from plasma concentrations of *d*- and *l*-amphetamine by non-compartmental techniques using WinNonlin® Professional Version 4.1 or higher. All calculations were based on actual sampling times.

Pharmacokinetic parameters to be calculated included (but would not necessarily be limited to): C_{max}, AUC_{0-t}, $AUC_{0-\infty}$, t_{max}, $t_{1/2elim}$, CL/F, CL/F/Wt, V_z/F, and V_z/F/Wt. Descriptive statistics (number of subjects, mean, SD, CV, median, minimum, and maximum) were used to summarize PK parameters (geometric mean used also for C_{max} and AUCs). Plots of individual subject and mean C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ by treatment were provided. Individual subject stripping plots illustrating the extrapolation of the concentration-time curve to obtain $AUC_{0-\infty}$ were also provided.

The statistical analysis of PK data followed the principles recommended by the FDA (2003).

Pharmacokinetic parameters were evaluated for *d*- and *l*-amphetamine following administration of Adderall XR capsules and Adderall tablets (Treatments A and B) compared to *d*- and *l*-amphetamine following administration of an oral solution of mixed amphetamine salts (Treatment C) with a mixed model analysis of variance of the natural log-transformed PK parameters from a three-way crossover design. The analysis using SAS® PROC MIXED with a random term for subject-within-sequence and fixed terms for sequence, period, and treatment were performed for the parameters C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$.

Exponentiated least squares mean test/reference ratios and 90% confidence intervals for the ratios were obtained. Treatments A and B were compared to Treatment C, with Treatment C as the reference. Bioequivalence between treatments was demonstrated if the 90% confidence intervals were within the 80-125% range.

Safety analyses

All AEs were coded using the MedDRA dictionary version 8.0.

Adverse event summaries only summarized treatment-emergent adverse events (TEAEs). An AE was considered treatment-emergent during treatment in Period 1 if it started on or after Period 1 dosing but prior to Period 2 dosing (on or prior to the last day of all subject dosing of Period 1 if the subject did not have a Period 2 dose). An AE was considered Treatment-Emergent during treatment in Period 2 if it started on or after Period 2 dosing but prior to Period 3 dosing (on or prior to the last day of all subject dosing of Period 2 if the subject did not have a Period 3 dose). An AE was considered Treatment-Emergent during

treatment in Period 3 if it started on or after Period 3 dosing through 60 hours postdose. Adverse events with partial start dates or completely missing start dates were considered as Treatment-Emergent to the respective period by using available non-missing information. If it could not be determined whether the AE was Treatment-Emergent, or if the period could not be determined, then the AE was considered as Treatment-Emergent in Period 1 (or the earliest possible period consistent with the partially missing values).

Treatment-emergent AEs were summarized by the number and percentage of subjects experiencing events by body system, preferred term, and treatment. A subject was counted only once within a given body system and preferred term combination.

Treatment-emergent AEs were also summarized by severity (mild, moderate, severe) and by relationship to study drug (not suspected, suspected), with subjects placed in the most severe or most related category of any TEAE within a given body system and preferred term combination. Treatment-emergent AEs leading to study withdrawal were summarized separately.

Separate listings were provided for all AEs and serious AEs.

Clinical Laboratory Assessments

Clinical laboratory data were presented using conventional units.

Descriptive statistics were provided to summarize quantitative clinical laboratory analytes for all subjects combined at Screening and End of Study.

A shift table was provided to summarize the frequency of subject changes from Screening Baseline low, normal, and high categories to End of Study low, normal, and high categories for each quantitative clinical laboratory analyte.

The incidence of potentially clinically important clinical laboratory values was summarized by analyte and visit. Hematology, biochemistry, and urinalysis outlier criteria are presented in Table 6, Table 7, and Table 8, respectively. Note that not all tests indicated in the study protocol may have associated outlier criteria.

Table 6: Hematology and Differential Outlier Criteria

Test Name	Outlier Criteria
Hemoglobin	<10g/dL
Platelet count	<75,000/mm^3 or >500,000mm^3
White Blood Cell Count (WBC)	<3000/mm^3 or >16,000mm^3
Neutrophils	<1500/mm^3 or <40%
Lymphocytes	<10% or >50%
Monocytes	>25%
Eosinophils	>10%

Table 7: Biochemistry Outlier Criteria

Test Name	Outlier Criteria
Bilirubin	>1.5 x ULN
Alkaline phosphatase	>2.5 x ULN (or alternatively >400U/L)
Transaminase, SGOT, AST	>2.5 x ULN
Transaminase, SGPT, ALT	>2.5 x ULN
Urea nitrogen (BUN)	>2.5 x ULN (or alternatively H >30mg/dL)
Creatinine, serum	>1.5 x ULN (or alternatively H >2mg/dL)
Glucose, blood	<55mg/dL or >160mg/dL
Calcium	<8mg/dL or >11.5mg/dL
Total protein, plasma or serum	<5g/dL or >9g/dL
Albumin	<3g/dL
Sodium	<130mmol/L (grade III) or >150mmol/L
Potassium, serum/plasma	<3mmol/L (grade III) or >5.5mmol/L
Bicarbonate	<16mmol/L or >30mmol/L
Uric acid, serum	>10mg/dL Males and >8mg/dL Females
Gamma Glutamyl Transpeptidase (GGT)	>2.5 X ULN
Phosphorus, inorganic	<2.5mg/dL or >5mg/dL
Lactate dehydrogenase (LDH)	>3 x ULN
Thyroid Stimulating Hormone (TSH)	<LLN or >2 x ULN
Cholesterol-H	>300mg/dL

Table 8: Urinalysis Outlier Criteria

Test Name	Outlier Criteria
Protein	≥2+
Glucose	≥1+
Blood	≥2+
Leukocyte Esterase	Present

Vital Signs

Descriptive statistics were provided to summarize vital signs (systolic and diastolic BP, HR, respiratory rate, and weight) and change from predose Baseline within each period by time point and treatment.

The incidence of vital signs outliers were summarized by time point and treatment. Vital signs outlier criteria are presented in Table 9. Note that not all tests indicated in the study protocol may have associated outlier criteria.

Table 9: Vital Signs Outlier Criteria

Test Name	Outlier Criteria
Systolic BP (mmHg)	<100 or >140
Diastolic BP (mmHg)	<60 or >90
Heart rate	≤50beats/minute or ≥100beats/minute
Weight	≥7% in body weight from Baseline (short term only)
Temperature (degrees C)	>39 or <35 (oral or tympanic)

Twelve-Lead Electrocardiograms

Descriptive statistics were provided to summarize ECG parameters (PR, QRS, QT, QTcB, QTcF, and HR) and change from predose Baseline within each period by time point and treatment.

The incidence of 12-lead ECG outliers was summarized by time point and treatment. Electrocardiogram outlier criteria are presented in Table 10.

Table 10: Electrocardiogram Outlier Criteria

Test Name	Outlier Criteria
ECG Overall Interpretation	Shift from a normal Baseline to an abnormal finding or from an abnormal Baseline to a new abnormal finding
Heart Rate	≤50beats/minute or ≥100 beats/minute
PR Interval	≥200msec
QT Interval	≥480msec
QRS Interval	≥120msec
QT/QTc	≥450msec and <480msec
	≥480msec and <500msec
	≥500msec
QT/QTc from Baseline	≥30msec and <60msec
	≥60msec
Rhythm	Any rhythm other than sinus rhythm

Physical Examinations

Physical examination data were listed.

5.7.1.5 Interim analysis

No interim analysis was planned or conducted for this study.

5.8 Changes in the Conduct of the Study or Planned Analyses

5.8.1 Clarifications to the protocol

5.8.1.1 Protocol clarifications and changes

Administrative clarifications and changes were summarized in a letter to the Principal Investigator on 01 July 2005, which was subsequently approved by Mid'Lands Institutional Review Board on 11 July 2005.

The original protocol (03 June 2005) indicated that medical history would be summarized by treatment group. Since all subjects receive all treatments in this three-period crossover design, medical history was only listed.

The original protocol indicated that clinical laboratory assessments would be summarized by treatment group. Since all subjects receive all treatments in this three-period crossover design and no clinical laboratory assessments were done during the individual study periods, clinical laboratory assessments were summarized for all subjects only and listed for each subject.

5.8.2 Changes to the statistical analysis plan

The final Statistical Analysis Plan (12 August 2005) indicated that listings would be provided for all TEAEs and serious TEAEs. Listings were provided for all AEs and serious AEs.

The final Statistical Analysis Plan indicated that clinical laboratory data would be reported in Système International (SI) units. Laboratory data were collected in conventional units and were reported in conventional units.

The final Statistical Analysis Plan indicated that that one of the potentially clinically important vital sign outlier criteria would be assessed for postural orthostatic BP change. Considering that all BPs obtained in this study were in the seated position only, no assessment of orthostatic change was possible, therefore no analysis was performed.

6. STUDY SUBJECTS - RESULTS

6.1 Time Period of Study

First subject enrolled: 28 June 2005
First subject randomised: 15 July 2005
First subject dosed: 15 July 2005
Last subject dosed: 29 July 2005
Last subject completed follow-up: 01 September 2005

6.2 Disposition of Subjects

A summary of subject disposition is presented in Table 11. A total of 18 subjects were enrolled and randomized into this study. One subject was discontinued from the study due to an adverse event. Seventeen subjects completed all three dosing periods. A summary of subject disposition is presented in Section 12.1, Table 1.1 and a listing of individual subject disposition is presented in Appendix 2, Listing 2.1.

Table 11: Subject Disposition for All Enrolled Subjects

	Sequence													
	ABC N (%)		ACB N (%)		BAC N (%)		BCA N (%)		CAB N (%)		CBA N (%)		Total N (%)	
Study Subjects:														
Randomized	3		3		3		3		3		3		18	
Safety Population	3	(100.0)	3	(100.0)	3	(100.0)	3	(100.0)	3	(100.0)	3	(100.0)	18	(100.0)
PK Population	3	(100.0)	3	(100.0)	3	(100.0)	3	(100.0)	3	(100.0)	3	(100.0)	18	(100.0)
Completed	3	(100.0)	2	(66.7)	3	(100.0)	3	(100.0)	3	(100.0)	3	(100.0)	17	(94.4)
Early Termination	0	(0.0)	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.6)
Primary Reason for Early Termination:														
Adverse Event(s)	0	(0.0)	1	(33.3)	0	(0.0)	0	(0.0)	0	(0.0)	0	(0.0)	1	(5.6)

Source: Section 12.1, Table 1.1

A=Adderall XR 30mg, B=Adderall 30mg, C=MAS [5mg/mL] x 6mL.

6.3 Demographic and Other Baseline Characteristics

A summary of dernographics and Baseline characteristics for the Safety population is provided in Section 12.1, Table 1.2 and in Table 12. A by-subject listing of demographic and Baseline characteristics is provided in Appendix 2, Listing 2.2.

Table 12: Subject Demographics and Baseline Characteristics (Safety Population)

		Sequence						
		ABC (N=3)	ACB (N=3)	BAC (N=3)	BCA (N=3)	CAB (N=3)	CBA (N=3)	Total (N=18)
Age (years)	Mean (SD)	27.7 (4.04)	25.7 (3.06)	41.7 (16.20)	28.7 (6.81)	48.7 (2.31)	31.7 (6.81)	34.0 (10.91)
	Median (min, max)	27.0 (24, 32)	25.0 (23, 29)	50.0 (23, 52)	31.0 (21, 34)	50.0 (46, 50)	34.0 (24, 37)	31.5 (21, 52)
Gender (%)	Male	3 (100.0)	3 (100.0)	3 (100.0)	2 (66.7)	2 (66.7)	1 (33.3)	14 (77.8)
	Female	0 (0.0)	0 (0.0)	0 (0.0)	1 (33.3)	1 (33.3)	2 (66.7)	4 (22.2)
Ethnicity (%)	Hispanic/Latino	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
	Not Hispanic/Latino	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	3 (100.0)	18 (100.0)
Race (%)	White	2 (66.7)	3 (100.0)	2 (66.7)	2 (66.7)	3 (100.0)	2 (66.7)	14 (77.8)
	Black/African American	1 (33.3)	0 (0.0)	0 (0.0)	1 (33.3)	0 (0.0)	1 (33.3)	3 (16.7)
	Other	0.(0.0)	0 (0.0)	1 (33.3)	0 (0.0)	0 (0.0)	0 (0.0)	1 (5.6)
Weight (kg)	Mean (SD)	85.6 (7.81)	72.1 (2.25)	81.8 (9.77)	71.3 (8.12)	72.0 (12.11)	60.3 (9.27)	73.9 (11.14)
	Median (min, max)	87.1 (77, 93)	72.1 (70, 74)	85.3 (71, 89)	67.1 (66, 81)	77.6 (58, 80)	63.5 (50, 68)	73.3 (50, 93)
Height (cm)	Mean (SD)	187.1 (6.40)	171.0 (3.92)	180.4 (6.73)	175.2 (8.78)	167.7 (9.17)	161.7 (8.15)	173.9 (10.57)
	Median (min, max)	188.0 (180, 193)	170.2 (168, 175)	177.8 (175, 188)	180.3 (165, 180)	170.2 (158, 175)	165.1 (152, 168)	175.3 (152, 193)
BMI (kg/m^2)	Mean (SD)	24.7 (3.85)	24.7 (0.44)	25.2 (2.74)	23.3 (2.54)	25.5 (1.76)	23.0 (1.33)	24.4 (2.21)
	Median (min, max)	24.7 (20.8, 28.5)	24.9 (24.2, 25.0)	24.2 (23.1, 28.3)	24.7 (20.4, 24.9)	26.2 (23.5, 26.8)	23.3 (21.5, 24.1)	24.5 (20.4, 28.5)

Source: Section 12.1, Table 1.2

A=Adderall XR 30mg, B=Adderall 30mg, C=MAS [5mg/mL] x 6mL.

6.4 Prior and Concomitant Therapy

A by-subject listing of prior and concomitant medications is provided in Appendix 2, Listing 2.6. Four subjects (1-405, 1-406, 1-415, and 1-434) received one or more prior medications before being randomized to study drug. All prescription and OTC drugs were to be discontinued within 7 days prior to Day -1. No subject received a prior medication that was continued during the study.

Three subjects (1-405, 1-422 and 1-444) received concomitant medication during the study. Subjects 1-405 and 1-422 received topical hydrocortisone to treat contact dermatitis. Subject 1-444 received a single 800mg dose of ibuprofen to treat a headache after receiving MAS.

6.5 Measurements of Treatment Compliance

Study site personnel conducted a mouth check after each administration of study drug to assure that each subject swallowed the study drug. All subjects received their assigned treatment in the assigned treatment sequence. Subject 1-419 was withdrawn after the first dosing period (Adderall XR) and did not receive MAS or Adderall in the second and third dosing periods, respectively. A by-subject listing of the investigational product dispensed is provided in Appendix 2, Listing 2.5.

6.6 Protocol Deviations

An individual by-subject listing of inclusion and exclusion criteria is provided in Appendix 2, Listing 2.3.1 and 2.3.2, respectively.

The protocol deviations that occurred in this study did not impact the overall study results. Subject 1-419 did not have an early termination ECG performed. Two subjects (1-421 and 1-414) arrived late to the clinic so vital signs were obtained after the PK blood draw for the 48 hour sample. Individual subject deviations can be found in Appendix 2, Listing 2.7

7. PHARMACOKINETIC - RESULTS

7.1 Data Sets Analyzed

All subjects who were included in Safety population and who had evaluable concentration-time profiles in at least one study period to determine both C_{max} and AUC parameters were to be included in the pharmacokinetic and statistical analyses. No subjects were excluded from the pharmacokinetic analyses (Appendix 2, Listing 2.1).

7.2 Drug Concentration Analysis

The computation of *d*- and *l*-amphetamine pharmacokinetic parameters employed actual plasma collection times. The amounts of each enantiomer in plasma were determined by a validated liquid chromatography with tandem mass spectrometry (LC/MS/MS). Details of the bioanalytical method are provided in Appendix 3.1. All quantifiable samples were included in statistical summaries of plasma concentrations.

7.3 Pharmacokinetic Results

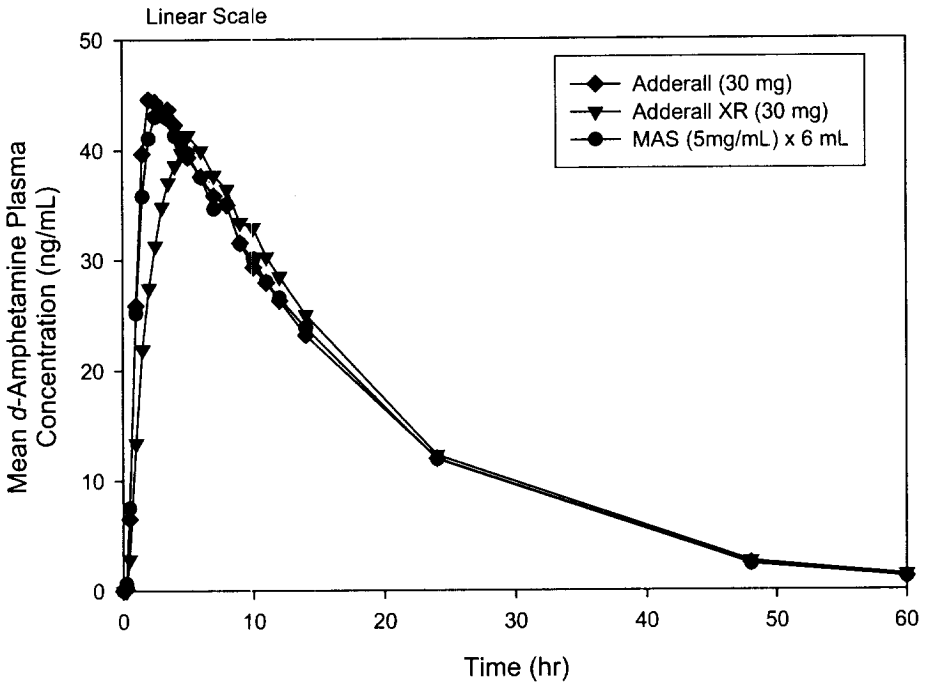
7.3.1 *d*-Amphetamine

7.3.1.1 Plasma concentrations of *d*-amphetamine

Section 12.1, Table 2.1 presents a descriptive statistics summary of *d*-amphetamine plasma concentrations in healthy volunteers who were dosed with Adderall XR 30mg, Adderall 30mg or MAS [5mg/mL] x 6mL. Individual subject *d*-amphetamine plasma concentrations are listed in Appendix 2, Listing 2.8.1 and the plasma concentrations versus time profiles are illustrated in Section 12.1, Figures 1.1 and 1.2, on linear and semi logarithmic scales, respectively.

Figure 2 shows, on a linear scale, the mean *d*-amphetamine plasma concentration-time profiles after a single oral dose of amphetamine formulation, ie either Adderall XR, Adderall or MAS. *d*-Amphetamine was quantifiable in plasma at the first sampling point (0.25 hour) after oral dosing and peaked between 2-4 and 2-4.5 hours in subjects who were dosed with Adderall and MAS, respectively. However, the compound peaked later, between 2.5 and 10 hours, in subjects receiving Adderall XR. Following peak levels, *d*-amphetamine disappeared from plasma in a monoexponential manner, generally parallel among each of the three treatments.

Figure 2: Mean *d*-Amphetamine Plasma Concentrations Over Time After a Single 30mg Amphetamine Dose to Healthy Subjects



Source: Section 12.1, Figure 1.1, Figure 1.2, Table 2.1

7.3.1.2 Pharmacokinetic parameters of *d*-amphetamine

Mean plasma pharmacokinetic parameters of *d*-amphetamine following an oral dose of amphetamine formulation are presented in Section 12.1, Table 2.2. Results from the statistical analysis between treatment periods are presented in Section 12.1, Table 2.3. Individual subject parameters are shown in Appendix 2, Listing 2.8.2. Table 13 and Table 14 summarize the comparative evaluation on key plasma pharmacokinetic parameters.

Table 13: *d*-Amphetamine Plasma Pharmacokinetic Parameters Following a Single 30mg Amphetamine Dose to Healthy Subjects

Parameter	Statistic	Treatment		
		Adderall XR (A)	Adderall (B)	MAS (C)
	N*	18	17	17
C_{max} (ng/mL)	Mean (SD)	44.0 (7.3)	46.2 (10.4)	45.4 (8.7)
T_{max} (hr)	Median (Min, Max)	5.0 (2.5, 10.0)	2.5 (2.0, 4.0)	3.0 (2.0, 4.5)
$T_{1/2elim}$ (hr)	Mean (SD)	10.9 (1.5)	10.8 (1.5)	10.5 (1.2)
$AUC_{0-\infty}$ (hr*ng /mL)	Mean (SD)	843.8 (120.0)	844.1 (102.3)	838.8 (136.3)
AUC_{0-t} (hr*ng /mL)	Mean (SD)	821.7 (118.4)	825.1 (100.7)	820.4 (135.5)
CL/F (L/hr)	Mean (SD)	27.1 (3.4)	27.1 (3.5)	27.6 (4.8)
CL/F/Wt (L/hr/kg)	Mean (SD)	0.4 (0.05)	0.4 (0.04)	0.4 (0.05)
Vz/F (L)	Mean (SD)	425.7 (77.4)	422.7 (77.8)	418.4 (85.3)
Vz/F/Wt (L/kg)	Mean (SD)	5.8 (0.7)	5.8 (1.1)	5.6 (0.6)

Source: Section 12.1, Table 2.2
(A) Adderall XR (30mg)
(B) Adderall (30mg)
(C) MAS [5mg/mL] x 6mL
* Subject 1-419 was withdrawn after the first dosing period (Adderall XR) and did not receive MAS or Adderall in the second and third dosing periods, respectively.

Table 14: Statistical Analysis Results of Plasma *d*-Amphetamine Following a Single 30mg Amphetamine Dose to Healthy Subjects

Parameter	N	Exponentiated LS Means			Ratio of LS Means		90% CI of LS Mean Ratio	
		Adderall XR (A)	Adderall (B)	MAS (C)	A/C	B/C	A/C	B/C
C_{max} (ng/mL)	18	43.4	45.2	44.7	97.1	101.0	92.5, 101.9	96.2, 106.0
$AUC_{0-\infty}$ (hr*ng /mL)	18	836.4	839.2	830.9	100.7	101.0	96.3, 105.2	96.6, 105.6
AUC_{0-t} (hr*ng/mL)	18	814.4	820.7	813.1	100.2	100.9	95.9, 104.6	96.7, 105.4

Source: Section 12.1 Table 2.3
(A) Adderall XR (30mg)
(B) Adderall (30mg)
(C) MAS [5mg/mL] x 6mL
LS=Least squares

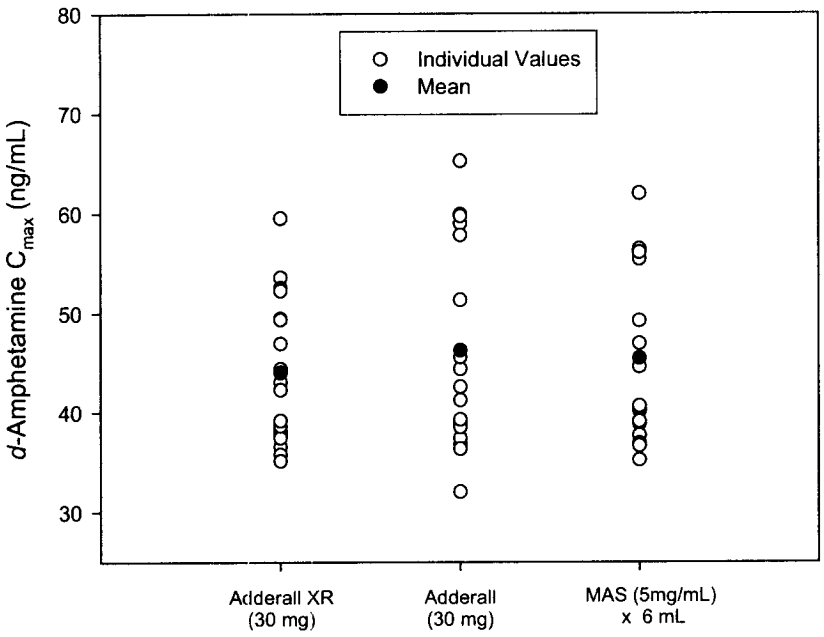
The exposure to *d*-amphetamine, as described by C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ was comparable between subjects administered with either Adderall XR, Adderall or MAS. The 90% confidence intervals (CI) of the test-to-reference ratios, with MAS oral solution as the reference treatment, were within the typically acceptable bioequivalence range of 80% to 125%. Additionally, The CI on the ratios between subjects receiving Adderall XR or Adderall against MAS were evenly distributed on either side of 100%. These observations indicate that the exposure to *d*-enantiomer after Adderall XR or Adderall dose was comparable to the exposure following MAS dose.

The individual values and means of *d*-amphetamine C_{max}, AUC_{0-t} and $AUC_{0-\infty}$ are presented in Section 12.1, Figures 4.1.1, 4.1.2, and 4.1.3; and Figure 3, Figure 4, and Figure 5.

The median time to maximum plasma concentrations, T_{max}, in subjects who were treated with Adderall and MAS was 2.5 and 3 hours, respectively. The T_{max} of subjects receiving Adderall XR was approximately 2 hours later with a median value of 5 hours.

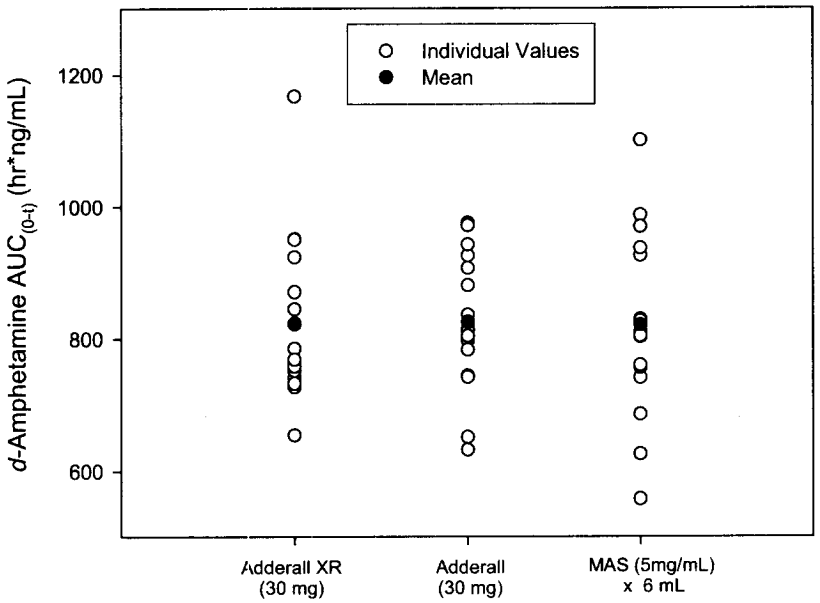
The elimination half-life of *d*-amphetamine, obtained from the terminal slopes of concentration-time plots (Section 12.1, Figures 1.1 and 1.2), was similar across Adderall XR, Adderall, and MAS treatments, and the mean values ranged between 10.5 –10.9 hours. The mean CL/F and Vz/F were similar in subjects receiving either Adderall XR or Adderall versus MAS. These values, when adjusted for individual body weight, remained comparable across these treatments.

Figure 3: Individual and Mean *d*-Amphetamine C_{max} Values After a Single 30mg Amphetamine Dose



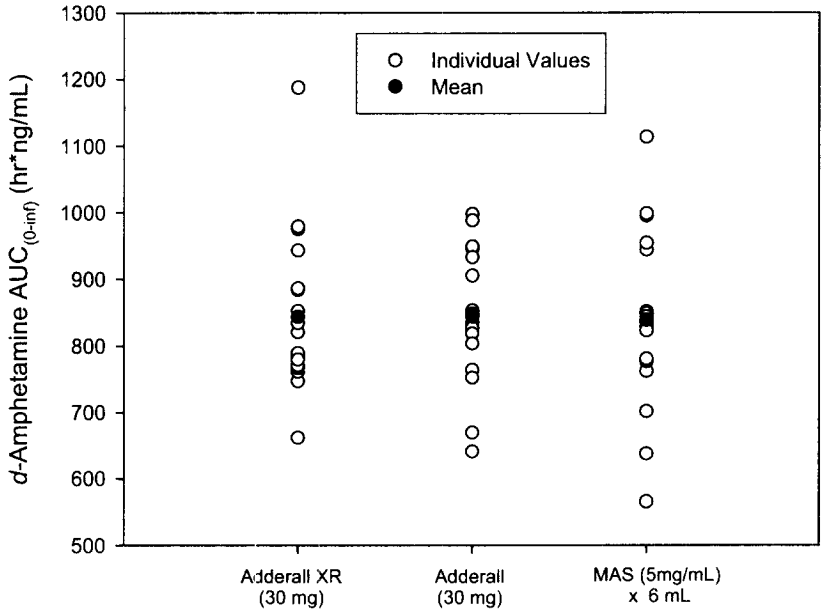
Source: Section 12.1, Figure 4.1.1, Table 2.2; Appendix 2, Listing 2.8.2

Figure 4: Individual and Mean *d*-Amphetamine AUC_{0-t} After a Single 30mg Amphetamine Dose



Source: Section 12.1, Figure 4.1.2, Table 2.2; Appendix 2, Listing 2.8.2

Figure 5: Individual and Mean *d*-Amphetamine $AUC_{0-\infty}$ After a Single 30mg Amphetamine Dose



Source: Section 12.1, Figure 4.1.3 Table 2.2; Appendix 2, Listing 2.8.2

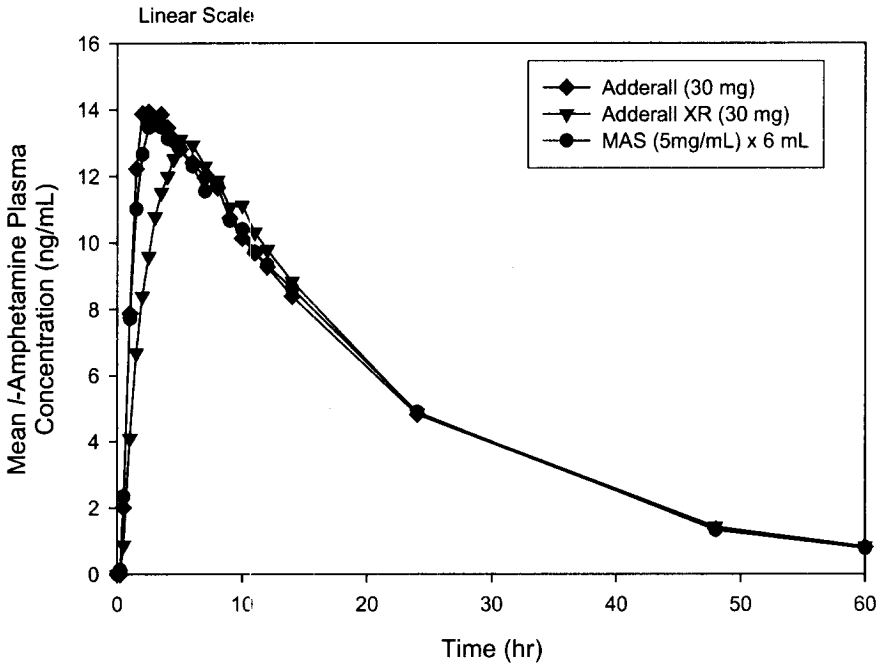
7.3.2 *l*-Amphetamine

7.3.2.1 Plasma concentrations of *l*-amphetamine

Section 12.1, Table 2.1 presents a descriptive statistics summary of *l*-amphetamine plasma concentrations in healthy volunteers who were dosed with Adderall XR 30mg, Adderall 30mg or MAS [5mg/mL] x 6mL. Individual subject *l*-amphetamine plasma concentrations are shown in Appendix 2, Listing 2.8.1 while plasma concentrations versus time profiles are illustrated in Section 12.1, Figures 2.1 and 2.2, on linear and semi logarithmic scales, respectively.

As shown in Figure 6 and unlike its *d*-enantiomer, *l*-amphetamine was quantifiable in plasma at the first sampling point (0.25 hour) only in subjects administered with MAS. However, similar to *d*-amphetamine, the compound peaked at an average of 3.4 and 3.2 hours after Adderall and MAS dosing, respectively, and 5.3 hours in subjects receiving Adderall XR (Section 12.1, Table 2.2). The compound disappeared from plasma in a monoexponential manner following peak concentrations in a manner similar to that seen with *d*-amphetamine.

Figure 6: Mean *l*-Amphetamine Plasma Concentrations Over Time After a Single 30mg Amphetamine Dose to Healthy Subjects



Source: Section 12 1, Figure 2.1, Figure 2.2, Table 2.1

7.3.2.2 Pharmacokinetic Parameters of *l*-Amphetamine

Mean plasma pharmacokinetic parameters of *l*-amphetamine following an oral Adderall XR, Adderall or MAS dose to healthy subjects are presented in Section 12.1, Table 2.2; statistical analysis results are presented in Section 12.1, Table 2.3. Individual subject parameters are presented in Appendix 2, Listing 2.8.2. Table 15 and Table 16 summarize the comparative evaluation on key plasma pharmacokinetic parameters.

Table 15: *l*-Amphetamine Plasma Pharmacokinetic Parameters Following a Single 30mg Amphetamine Dose to Healthy Subjects

Parameter	Statistic	Treatment		
		Adderall XR (A)	Adderall (B)	MAS (C)
	N*	18	17	17
C_{max} (ng/mL)	Mean (SD)	14.0 (2.5)	14.6 (3.2)	14.3 (2.8)
T_{max} (hr)	Median (Min, Max)	5.0 (3.0, 10.0)	2.5 (2.0, 10.0)	3.0 (2.5, 4.5)
$T_{1/2elim}$ (hr)	Mean (SD)	13.6 (2.2)	13.6 (2.2)	13.1 (1.8)
$AUC_{0-\infty}$ (hr*ng /mL)	Mean (SD)	315.2 (51.9)	318.5 (49.1)	318.0 (61.3)
AUC_{0-t} (hr*ng /mL)	Mean (SD)	297.6 (49.6)	302.2 (46.6)	302.3 (59.7)
CL/F (L/hr)	Mean (SD)	24.3 (3.5)	24.1 (4.0)	24.4 (4.8)
CL/F/Wt (L/hr/kg)	Mean (SD)	0.3 (0.05)	0.3 (0.05)	0.3 (0.05)
Vz/F (L)	Mean (SD)	474.4 (88.1)	471.0 (90.8)	460.1 (96.5)
Vz/F/Wt (L/kg)	Mean (SD)	6.4 (0.8)	6.4 (1.3)	6.2 (0.8)

Source: Section 12.1, Table 2.2
(A) Adderall XR (30mg)
(B) Adderall (30mg)
(C) MAS [5mg/mL] x 6mL
* Subject 1-419 was withdrawn after the first dosing period (Adderall XR) and did not receive MAS or Adderall in the second and third dosing periods, respectively.

Table 16: Statistical Analysis Results of Plasma *l*-Amphetamine Following a Single 30mg Amphetamine Dose to Healthy Subjects

Parameter	N	Exponentiated LS Means			Ratio of LS Means		90% CI of LS Mean Ratio	
		Adderall XR (A)	Adderall (B)	MAS (C)	A/C	B/C	A/C	B/C
C_{max} (ng/mL)	18	13.8	14.3	14.1	97.7	101.6	92.8, 102.9	96.5, 106.9
$AUC_{0-\infty}$ (hr*ng /mL)	18	311.6	314.2	312.4	99.7	100.6	94.9, 104.8	95.7, 105.7
AUC_{0-t} (hr*ng/mL)	18	294.2	298.5	297.3	99.0	100.4	94.3, 103.9	95.6, 105.4

Source: Section 12.1, Tables 2.3
(A) Adderall XR (30mg)
(B) Adderall (30mg)
(C) MAS [5mg/mL] x 6mL
LS=Least squares

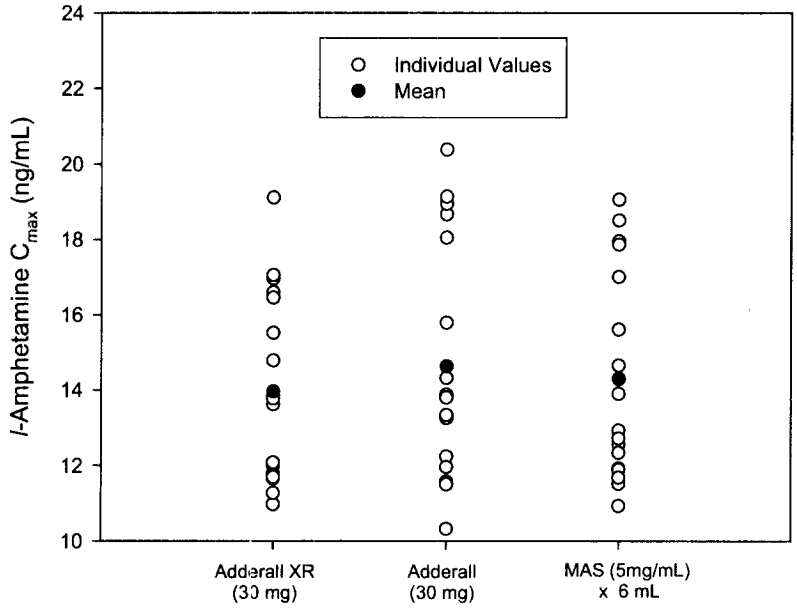
l-Amphetamine C_{max}, AUC_{0-t}, and $AUC_{0-\infty}$ were comparable between all three treatments. As observed for *d*-amphetamine, the 90% CI of the test-to-reference ratios of least squares (LS) means were within the typically acceptable bioequivalence range of 80% to 125%. Again similar to *d*-amphetamine, the CI on the ratios between subjects receiving either Adderall XR or Adderall against those receiving MAS as a reference treatment were evenly distributed on either side of 100%. These observations indicate that the exposure to *l*-enantiomer after Adderall XR or Adderall dose was similar to the exposure following MAS dose.

Section 12.1, Figures 4.2.1, 4.2.2, and 4.2.3 and Figure 7, Figure 8, and Figure 9 illustrate the mean and individual values of *l*-amphetamine C_{max}, AUC_{0-t} and $AUC_{0-\infty}$, respectively, when amphetamine was administered to subjects as either of the three formulations.

The median time to maximum plasma concentrations, T_{max}, in subjects who were treated with Adderall and MAS was 2.5 and 3 hours, respectively. Parallel to its *d*-enantiomer, *l*-amphetamine T_{max} in subjects receiving Adderall XR was approximately 2 hours later with a median value of 5 hours.

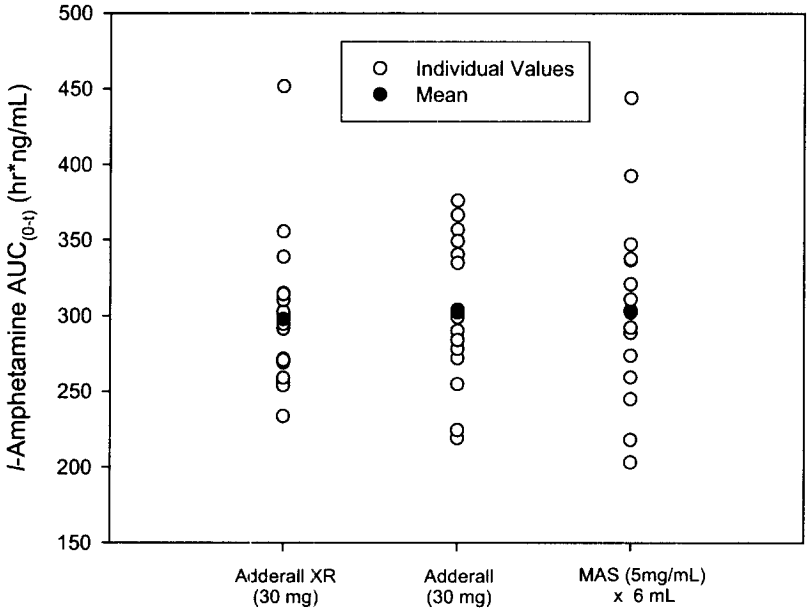
As observed with *d*-amphetamine, the elimination half-life of *l*-amphetamine, obtained from the terminal slopes of concentration-time plots (Section 12.1, Figures 2.1 and 2.2), was similar across Adderall XR, Adderall, and MAS treatments, and the mean values ranged between 13.1 –13.6 hours. *l*-amphetamine CL/F and Vz/F were similar in subjects receiving either Adderall XR or Adderall versus MAS. The weight adjusted CL/F and Vz/F values were also similar between following treatment with Adderall XR, Adderall, and MAS.

Figure 7: Individual and Mean *l*-Amphetamine C_{max} Values After a Single 30mg Amphetamine Dose



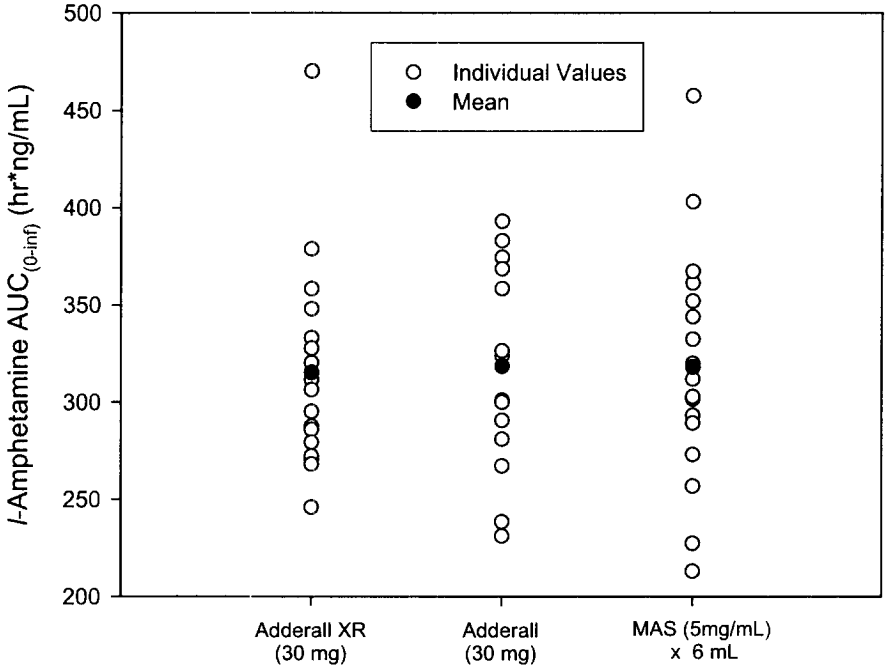
Source: Section 12.1, Figure 4.2.1, Table 2.2; Appendix 2, Listing 2.8.2

Figure 8: Individual and Mean *l*-Amphetamine AUC_{0-t} After a Single 30mg Amphetamine Dose



Source: Section 12.1, Figure 4.2.2, Table 2.2; Appendix 2, Listing 2.8.2

Figure 9: Individual and Mean *l*-Amphetamine $AUC_{0-\infty}$ After a Single 30mg Amphetamine Dose



Source: Section 12.1, Figure 4.2.3, Table 2.2; Appendix 2, Listing 2.8.2

7.4 Pharmacokinetic Conclusions

- The exposures to both *d*- and *l*-amphetamine as assessed by C_{max} and AUC values from healthy subjects following either Adderall XR or Adderall dosing was comparable to the exposure after MAS treatment. The 90% confidence intervals for the ratios of LS means were contained entirely within the typically accepted bioequivalence range of 80-125%.
- In comparing plasma concentration-time profiles, time to maximum plasma concentrations of both the *d*- and *l*-isomers was comparable between Adderall and MAS treatments. However, C_{max} occurred approximately 2 hours later for the Adderall XR treatment.
- The Vz/F and CL/F of both *d*- and *l*-amphetamine was similar during the Adderall XR, Adderall, and MAS treatment periods.

8. SAFETY EVALUATION - RESULTS

8.1 Extent of Exposure

Seventeen of the 18 randomized subjects received all assigned study drug treatments. Each single dose administration was separated by at least a 7-day washout period. Subject 1-419 was withdrawn due ST-T wave abnormalities observed on an ECG obtained approximately 5 hours after Adderall XR dosing during the first treatment period, as described in Section 8.3.5, and therefore did not receive MAS or Adderall.

8.2 Adverse Events

All AEs were recorded from the time the informed consent was signed until the end of treatment exposure. A TEAE was defined as an AE with an onset after study drug administration through 60 hours postdose of the last treatment the subject received in the study. Adverse events with missing start dates were assumed to be treatment-emergent. The MedDRA version 8.0 was used to code the reported AEs by System Organ Class. A by-subject listing of AEs is provided in Appendix 2, Listing 2.9.

8.2.1 Brief summary of adverse events

Seventeen of 18 subjects (94.4%) reported one or more TEAEs during the study. A total of 73 TEAEs were reported. The percentage of subjects reporting a TEAE was generally similar during each Adderall XR (72.2%), Adderall (64.7%), and MAS (70.6%) treatment period.

Forty of the 73 reported TEAEs (54.8%) were considered by the Investigator as having a suspected relationship to study drug. The Investigator considered all other TEAEs as not suspected to be related (33/73, 45.2%) to study drug. The most common TEAEs that were considered as having a suspected relationship to study drug were palpitations, dry mouth, hypervigilance, and vision blurred. The majority of TEAEs were considered by the Investigator to be mild (59/73, 80.8%) in intensity. All AEs resolved before the subject was discharged from the study.

No subjects died and no subjects reported an SAE. One subject was withdrawn from the study due to an abnormality noted on two ECGs. Subsequent to the subject's withdrawal, the central over-read of the ECGs found them to be normal.

8.2.2 Description and analysis of adverse events

8.2.2.1 Most common adverse events

A summary of all TEAEs for subjects in the Safety population is provided in Section 12.1, Table 3.1. Table 17 presents a summary of the most commonly reported TEAEs regardless of causality or severity that occurred in more than one subject during treatment with

Adderall XR, Adderall, or MAS. The most commonly reported TEAEs were contact dermatitis, palpitations, and dry mouth. The percentage of subjects reporting treatment-emergent contact dermatitis was highest following Adderall XR treatment. All instances of contact dermatitis were located on the chest and related to ECG lead placement. The percentage of subjects with treatment-emergent palpitations was higher during the MAS treatment period in comparison to the Adderall XR and Adderall treatment periods. The percentage of subjects with treatment-emergent dry mouth was higher during the Adderall and MAS treatment periods in comparison to the Adderall XR treatment period. A higher percentage of subjects reported headache and hypervigilance during the MAS treatment period compared to the Adderall XR and Adderall treatment periods.

Table 17: Most Commonly Reported Treatment-Emergent Adverse Events (reported by more than one subject during any treatment)

	Number (%) of subjects reporting AE					
Adverse Event (Preferred Term)	Adderall XR (N=18)		Adderall (N=17)		MAS (N=17)	
No. subjects with ≥1 AE	13	(72.2)	11	(64.7)	12	(70.6)
Dermatitis contact	4	(22.2)	1	(5.9)	3	(17.6)
Palpitations	2	(11.1)	2	(11.8)	3	(17.6)
Dry mouth	1	(5.6)	2	(11.8)	2	(11.8)
Headache	0	(0.0)	1	(5.9)	3	(17.6)
Hypervigilance	0	(0.0)	1	(5.9)	3	(17.6)
Vision blurred	2	(11.1)	0	(0.0)	1	(5.9)
Dizziness	2	(11.1)	0	(0.0)	0	(0.0)

Source: Section 12.1, Table 3.1

8.2.2.2 Severity of adverse events

An individual subject listing of all AEs is provided in Appendix 2, Listing 2.9. The majority of TEAEs were considered by the Investigator to be mild (59/73, 80.8%) in intensity. Twelve (16.4%) TEAEs were considered to be moderate in intensity. Two TEAEs (2.7%) were considered by the Investigator to be severe in intensity. Both severe TEAEs were reported by the same subject. Subject 1-420 reported severe muscle spasms approximately 19.5 hours after receiving Adderall XR and severe abdominal pain approximately 25 hours after receiving MAS. Both events resolved within 24 hours and were not suspected to be related to study drug by the Investigator.

A summary of TEAEs by severity (intensity) is provided in Section 12.1, Table 3.2. Subjects with more than one AE per body system or preferred term category are presented by only the most severe. The percentage of subjects reporting mild, moderate, and severe TEAEs was similar during each Adderall XR, Adderall, and MAS treatment period.

8.2.2.3 Relationship of adverse events to treatment

A summary of TEAEs by relationship to study drug is provided in Section 12.1, Table 3.3. An individual subject listing of all AEs is provided in Appendix 2, Listing 2.9. Forty of the 73 reported TEAEs (54.8%) were considered by the Investigator as having a suspected relationship to study drug. The Investigator considered all other TEAEs as not suspected to be related (33/73, 45.2%) to study drug.

The percentage of subjects with TEAEs that were suspected to be related to study drug was the same during the Adderall (23.5%) and MAS (23.5%) treatment periods, but higher than during the Adderall XR (16.7%) treatment period.

The most common TEAEs that were considered as having a suspected relationship to study drug were palpitations, dry mouth, hypervigilance, and vision blurred. All TEAEs of palpitations, dry mouth, hypervigilance, and vision blurred were considered by the Investigator as having a suspected relationship to study drug. The percentage of subjects with treatment-emergent palpitations was higher during the MAS (17.6%) treatment period in comparison to the Adderall XR (11.1%) and Adderall (11.8%) treatment periods. The percentage of subjects with treatment-emergent dry mouth was higher during the Adderall (11.8%) and MAS (11.8%) treatment periods in comparison to the Adderall XR (5.6%) treatment period. The percentage of subjects with treatment-emergent hypervigilance was higher during the MAS (17.6%) treatment period in comparison to the Adderall XR (0.0%) and Adderall (5.9%) treatment periods. The percentage of subjects with treatment-emergent vision blurred was higher during the Adderall XR (11.1%) treatment period in comparison to the Adderall (0.0%) and MAS (5.9%) treatment periods. All contact dermatitis AEs were not suspected to be related to study drug.

8.3 Deaths, Other Serious Adverse Events, Discontinuations due to Adverse Events and Other Significant Adverse Events

8.3.1 Deaths

No deaths occurred in this study (Appendix 2, Listing 2.10).

8.3.2 Other serious adverse events

No serious AEs occurred in this study (Appendix 2, Listing 2.10).

8.3.3 Discontinuations due to adverse events

A summary of TEAEs leading to study withdrawal for all subjects in the Safety population is presented in Section 12.1, Table 3.4. One subject (1-419) discontinued from the study due to an AE. Subject 1-419 was discontinued from the study due to ECG ST-T segment abnormalities after receiving Adderall XR during the first treatment period and did not receive MAS or Adderall in the second and third treatment periods, respectively. A narrative summary for this subject can be found in Section 8.3.5.3.

8.3.4 Other significant adverse events

Subject 1-406 had a TEAE of postural dizziness and Subject 1-414 had a TEAE of transient prolongation of the QTc interval. Individual subject narratives of these AEs can be found in Section 8.3.5.4.

8.3.5 Narratives of deaths, other serious adverse events, discontinuations due to adverse events and certain other significant adverse events

8.3.5.1 Deaths

No deaths occurred during this study.

8.3.5.2 Other serious adverse events

No SAEs occurred during this study.

8.3.5.3 Discontinuations due to adverse events

Subject 1-419, a 23 year old White male with an unremarkable medical history, was discontinued from the study due to ECG ST-T segment abnormalities. During the first treatment period (Adderall XR), on the 5.25 and 6 hour postdose ECG recordings, the Investigator suspected clinically significant inferolateral ischemia as evidenced by ST segment depressions and flipped T waves. All other ECGs collected during this treatment period were either normal or the abnormalities were considered not clinically significant. As per the protocol, all ECGs were over-read by a central reader. However, the central over-read of the two ECGs suspected to be abnormal by the Investigator was not completed before the scheduled study drug dosing for the second treatment period, therefore the subject was discontinued from the study. The subsequent central over-read of the two suspected abnormal ECGs was found to be normal. The subject did not receive the second (MAS) or third (Adderall) treatments. The AE was considered by the Investigator to be moderate in intensity and as having a suspected relationship to study drug. The subject did not report any other AEs during the study. A follow-up exercise echocardiogram performed by a cardiologist was normal without evidence of ischemia.

8.3.5.4 Other significant adverse events

Subject 1-406, a 21 year old White male with an unremarkable medical history, was reported as having mild postural dizziness beginning approximately 26 hours after receiving 30mg Adderall XR. During the first (Adderall) and second (MAS) treatment periods, the subject's BP and HR did not fall below the lower limit of normal and no AEs were reported. During the third treatment period, where the AE of postural dizziness was reported, the subject's predose BP and HR were 106/71mmHg and 75bpm, respectively. At approximately 2 hours prior to the AE, the subject's BP and HR were 101/68mmHg and 109bpm, respectively. The AE of postural dizziness was considered by the Investigator to be mild in intensity and not

suspected to be related to study drug. The event was reported to have resolved approximately 7 hours after it began. The subject did not receive any concomitant medications during the study.

Subject 1-414, a 46 year old White male with an unremarkable medical history except for multiple broken bones and surgeries from sports-related injuries, was reported as having mild transient prolongation of the QTc interval beginning approximately 90 minutes after receiving 30mg Adderall XR. The AE of transient QTc interval prolongation was considered by the Investigator to be mild in intensity and not suspected to be related to study drug. The QTc prolongation was reported to have resolved at the same time it occurred. The subject did not receive any concomitant medications during the study. The subject also reported an AE of mild anxiety at approximately the same time as the QTc interval prolongation was reported. The duration of the anxiety was approximately 3 hours and resolved without treatment. The anxiety was considered by the Investigator to be mild in intensity and suspected to be related to study drug. A summary of the QT, QTcB, and QTcF intervals for this subject are provided in Table 18.

Table 18: Summary of QT, QTcB, and QTcF Intervals for Subject 1-414

	Treatment Period								
	MAS			Adderall XR			Adderall		
	QT	QTcB	QTcF	QT	QTcB	QTcF	QT	QTcB	QTcF
Predose	477	404	427	457	402	419	437	398	410
0.75 hours postdose	493	394	424	450	402	418	419	405	410
1.5 hours postdose	477	433	447	467	516	499	377	472	438
2.25 hours postdose	446	408	421	432	469	456	407	455	438
3 hours postdose	448	405	419	428	399	408	391	424	413
3.75 hours postdose	430	406	414	414	427	423	377	427	410
4.5 hours postdose	362	422	401	387	409	402	361	429	405
5.25 hours postdose	380	413	402	352	407	388	338	434	399
6 hours postdose	388	408	401	355	415	394	328	434	395
7.5 hours postdose	353	408	389	376	429	411	340	441	405
9 hours postdose	334	443	404	377	427	410	348	414	391
10.5 hours postdose	352	414	392	343	429	398	370	342	351
12 hours postdose	360	419	398	359	419	398	348	427	399
24 hours postdose	441	414	423	446	452	450	400	408	405
48 hours postdose	403	488	458	420	429	426	387	426	413
60 hours postdose	403	418	413	398	456	436	362	481	438

Source: Appendix 2, Listing 2.13

8.3.6 Analysis and discussion of deaths, other serious adverse events, discontinuations due to adverse events and other significant adverse events

No subject died or reported an SAE during the study.

One subject was reported as having an AE that led to study withdrawal. The subject was suspected by the Investigator as having clinically significant inferolateral ischemia as evidenced by ST segment depressions and flipped T waves on two ECGs and was discontinued from the study. The subsequent central over-read of the suspected abnormal ECGs found them to be normal.

8.4 Clinical Laboratory Evaluation

8.4.1 Brief summary of laboratory parameters findings

There were no clinically meaningful differences in mean hematology, biochemistry, or urinalysis values between Screening and End of Study/Withdrawal during each Adderall XR, Adderall, or MAS treatment period.

No postdose abnormal laboratory values were considered by the investigator to be clinically significant and there were no laboratory AEs.

8.4.2 Laboratory values over time

A summary of hematology, biochemistry, and urinalysis values at Screening and End of Study/Withdrawal for subjects in the Safety population is provided in Section 12.1, Table 3.5. Individual subject laboratory results are presented in Appendix 2, Listing 2.11. There were no clinically meaningful differences in mean hematology, biochemistry, or urinalysis values between Screening and End of Study/Withdrawal during each Adderall XR, Adderall, or MAS treatment period.

8.4.3 Individual subject changes

8.4.3.1 Hematology

A summary of shifts in hematology values from Screening to End of Study for subjects in the Safety population is provided in Section 12.1, Table 3.6. No trends were exhibited in shifts of hematology values from Screening to End of Study other than the expected decrease in hemoglobin, hematocrit, and RBCs, based on the required blood draws associated with the study.

8.4.3.2 Biochemistry

A summary of shifts in biochemistry values from Screening to End of Study for subjects in the Safety population is provided in Section 12.1, Table 3.6. No medically important trends were exhibited in shifts of biochemistry values from Screening to End of Study.

8.4.3.3 Urinalysis

A summary of shifts in urinalysis values from Screening to End of Study for subjects in the Safety population is provided in Section 12.1, Table 3.6. No medically important trends were exhibited in shifts of urinalysis values from Screening to End of Study.

8.4.4 Individual clinically significant abnormalities

8.4.4.1 Hematology

A summary of potentially clinically important hematology outlier values in the Safety population is provided in Section 12.1, Table 3.7. Subject 1-429 had a potentially clinically important low neutrophil count (<40%) at Screening (33.8%) and End of Study (29%). This subject also had a potentially clinically important high lymphocyte count (>50%) at Screening (54.8%) and End of Study (59%). Subject 1-444 had a potentially clinically important high eosinophil count (>10%) at Screening (16%). None of these potentially clinically important hematology values were considered to be clinically significant by the Investigator and none were reported as AEs.

8.4.4.2 Biochemistry

A summary of potentially clinically important biochemistry outlier values in the Safety population is provided in Section 12.1, Table 3.7. No subject had a potentially clinically important biochemistry outlier value based on the criteria presented in Table 7. No post-treatment biochemistry values were considered to be clinically significant by the Investigator.

Subject 1-444 had a potassium value at Screening of 5.5mEq/L that was considered to be clinically significant by the Investigator. A repeat test performed 3 days later showed the subject's potassium level to be 4.5mEq/L and within normal limits (3.8-5.0mEq/L).

8.4.4.3 Urinalysis

A summary of potentially clinically important urinalysis outlier values in the Safety population is provided in Section 12.1, Table 3.7. No subject had a potentially clinically important urinalysis outlier value based on the criteria presented in Table 8. No urinalysis values were considered to be clinically significant by the Investigator.

8.5 Other Safety Data

8.5.1 Physical examination

A full physical examination was to be performed at Screening and End of Study/Withdrawal. Individual subject physical examination results are presented in Appendix 2, Listing 2.14. No clinically significant physical examination abnormalities were noted by the Investigator.

8.5.2 Vital signs

Measurements of vital signs (sitting systolic and diastolic BP, HR, and respiratory rate) were to be performed at Screening, Check-in for each treatment period, prior to study drug dosing, and at 1, 2, 3, 4, 5, 6, 7, 8, 9, 10, 11, 12, 24, 48, and 60 hours following study drug dosing. Body weight and temperature were to be performed at Screening, each Check-in, and End of Study/Withdrawal.

As previously discussed in Section 5.6.2, Subject 1-410 had an unscheduled vital signs CRF page that was found at the study site during the study closeout visit, post-database lock. During Period 1 (Adderall XR) at 48 hours postdose (0749), the subject had a BP of 118/76mmHg, a HR of 48bpm, and a respiration rate of 16breaths/minute. At 0840, a repeat unscheduled vital signs measurement was performed and the subject had a BP of 133/84mmHg, a HR of 69bpm, and a respiration rate of 18breaths/minutes. These were the vital signs contained on the missing CRF page and do not affect the vital signs data for the subject or the entire group.

8.5.2.1 Vital signs over time

A summary of vital signs for subjects in the Safety population is provided in Section 12.1, Table 3.8. Individual subject vital sign results are presented in Appendix 2, Listing 2.12.

A summary of mean change from Baseline (predose) in systolic BP over time is presented in Table 19. There was an increase in mean systolic BP relative to Baseline at all postdose time points during the Adderall XR treatment period and up to 24 hours postdose during the Adderall and MAS treatment periods. The increases in mean systolic BP were generally similar during the Adderall and MAS treatment periods. There was a larger increase in mean systolic BP relative to Baseline between 4 and 9 hours postdose during the Adderall XR treatment period compared to the Adderall and MAS treatment periods. The maximum mean changes from Baseline in systolic BP were seen at 2 hours postdose during the Adderall XR (+15.7mmHg) and Adderall (+18.8mmHg) treatment periods and one hour postdose during the MAS (+16.2mmHg) treatment period. The transient changes noted in systolic BP were not clinically significant.

Table 19: Mean (SD) Change from Baseline in Systolic Blood Pressure (mmHg) Values – Safety Population

	Adderall XR (N=18)	Adderall (N=17)	MAS (N=17)
Mean Baseline	111.1 (10.36)	111.5 (9.02)	113.8 (9.55)
1 hour postdose	11.3 (9.82)	17.3 (12.11)	16.2 (13.58)
2 hours postdose	15.7 (10.37)	18.8 (8.92)	15.3 (10.94)
3 hours postdose	15.6 (12.12)	15.5 (8.49)	14.5 (9.14)
4 hours postdose	14.3 (11.52)	10.2 (6.14)	9.4 (8.48)
5 hours postdose	14.3 (11.14)	10.5 (6.80)	7.9 (8.58)
6 hours postdose	10.0 (12.02)	7.0 (9.55)	6.4 (9.29)
7 hours postdose	10.4 (9.38)	9.2 (6.15)	7.9 (9.10)
8 hours postdose	12.6 (8.82)	10.0 (8.99)	8.8 (9.08)
9 hours postdose	12.4 (8.65)	9.1 (7.76)	5.1 (8.43)
10 hours postdose	11.8 (10.19)	11.0 (7.38)	10.5 (10.17)
11 hours postdose	9.9 (9.21)	10.2 (5.89)	6.9 (7.24)
12 hours postdose	8.5 (7.07)	8.1 (8.56)	6.2 (11.95)
24 hours postdose	3.8 (7.01)	1.5 (6.33)	2.0 (7.75)
48 hours postdose	1.4 (9.21)	-0.1 (8.45)	-0.8 (6.48)
60 hours postdose	5.7 (10.32)	5.1 (10.03)	1.5 (9.64)

Source: Section 12.1, Table 3.8

A summary of mean change from Baseline (predose) in diastolic BP over time is presented in Table 20. Similar to systolic BP, there was an increase in mean diastolic BP relative to Baseline at all postdose time points during the Adderall XR treatment period and up to 24 hours postdose during the Adderall and MAS treatment periods. The increases in mean diastolic BP were generally similar during the Adderall and MAS treatment periods. There tended to be a slightly larger increase in mean diastolic BP relative to Baseline during the Adderall XR treatment period compared to the Adderall and MAS treatment periods. The maximum mean changes from Baseline in diastolic BP were seen at 4 hours postdose during the Adderall XR (+9.1mmHg) treatment period and at 2 hours postdose during the Adderall (+9.1mmHg) and MAS (+10.5mmHg) treatment periods. The transient changes noted in diastolic BP were not clinically significant.

Table 20: Mean (SD) Change from Baseline in Diastolic Blood Pressure (mmHg) Values – Safety Population

	Adderall XR (N=18)	Adderall (N=17)	MAS (N=17)
Mean Baseline	71.5 (7.52)	73.3 (7.16)	73.3 (6.61)
1 hour postdose	7.4 (6.90)	6.2 (8.10)	7.0 (6.70)
2 hours postdose	8.9 (7.21)	9.1 (6.11)	10.5 (4.47)
3 hours postdose	8.0 (7.05)	6.2 (5.65)	7.2 (5.67)
4 hours postdose	9.1 (8.65)	4.5 (4.72)	4.6 (6.50)
5 hours postdose	5.0 (6.82)	1.9 (4.90)	3.9 (6.62)
6 hours postdose	4.1 (6.40)	2.6 (6.58)	2.0 (7.16)
7 hours postdose	3.8 (7.41)	3.3 (5.44)	3.1 (5.35)
8 hours postdose	6.6 (7.84)	4.8 (6.84)	5.2 (4.94)
9 hours postdose	7.3 (7.21)	4.1 (5.87)	4.6 (6.32)
10 hours postdose	6.2 (5.32)	2.7 (5.43)	5.1 (5.04)
11 hours postdose	3.8 (7.00)	3.4 (5.58)	3.2 (5.96)
12 hours postdose	5.3 (7.45)	3.1 (4.86)	2.2 (5.55)
24 hours postdose	4.8 (5.77)	1.1 (5.16)	2.2 (4.19)
48 hours postdose	1.8 (7.62)	-0.9 (6.13)	0.0 (4.70)
60 hours postdose	1.6 (6.36)	-0.6 (4.39)	-0.7 (6.32)

Source: Section 12.1, Table 3.8

A summary of mean change from Baseline (predose) in HR over time is presented in Table 21. There was an increase in mean HR relative to Baseline at most postdose time points during each Adderall XR, Adderall, and MAS treatment period. The increases in mean HR were generally similar during each Adderall XR, Adderall, and MAS treatment period. The maximum mean changes from Baseline in HR were seen at 6 hours postdose during the Adderall XR (+16.2bpm) and Adderall (+22.0bpm) treatment periods and at 11 hours postdose during the MAS (+19.3bpm) treatment period. The changes noted in HR were not clinically significant.

Table 21: Mean (SD) Change from Baseline in Heart Rate (bpm) Values – Safety Population

	Adderall XR (N=18)	Adderall (N=17)	MAS (N=17)
Mean Baseline	69.3 (13.01)	63.5 (8.74)	65.4 (10.44)
1 hour postdose	-0.8 (13.08)	4.4 (8.23)	4.9 (7.68)
2 hours postdose	2.3 (10.61)	7.5 (8.01)	4.1 (5.43)
3 hours postdose	3.3 (12.98)	7.6 (9.16)	7.5 (6.98)
4 hours postdose	5.0 (11.82)	10.9 (10.36)	8.6 (5.61)
5 hours postdose	13.4 (12.33)	19.1 (10.98)	15.0 (10.34)
6 hours postdose	16.2 (8.33)	22.0 (11.83)	15.6 (10.89)
7 hours postdose	12.7 (7.52)	15.3 (12.62)	16.6 (9.43)
8 hours postdose	10.2 (10.55)	15.8 (9.78)	15.5 (8.26)
9 hours postdose	9.6 (11.14)	15.9 (10.38)	12.6 (11.58)
10 hours postdose	13.1 (9.17)	16.4 (9.72)	17.6 (9.68)
11 hours postdose	16.0 (11.92)	19.1 (13.46)	19.3 (10.23)
12 hours postdose	14.2 (12.53)	20.4 (10.92)	16.1 (7.77)
24 hours postdose	8.9 (12.98)	13.0 (8.62)	15.3 (10.47)
48 hours postdose	2.1 (15.78)	8.9 (8.92)	6.0 (7.55)
60 hours postdose	3.6 (12.34)	8.5 (5.97)	10.1 (9.89)

Source: Section 12.1, Table 3.8

There were no notable differences in mean respiration rate relative to Baseline between the Adderall XR, Adderall, and MAS treatment periods.

No notable change in weight was observed between Screening and End of Study.

8.5.2.2 Individual subject vital sign changes

A summary of vital sign outliers is presented in Section 12.1, Table 3.9. Individual subject vital sign results are presented in Appendix 2, Listing 2.12. The number of subjects with potentially clinically important low (<100mmHg) and high (>140mmHg) systolic BP values was small and generally similar during the Adderall XR, Adderall, and MAS treatment periods. Similarly, the number of subjects with potentially clinically important low (<60mmHg) and high (>90mmHg) diastolic BP values was small and generally similar during the Adderall XR, Adderall, and MAS treatment periods.

The number of subjects with potentially clinically important low (≤50bpm) and high (≥100bpm) HRs was small and generally similar during the Adderall XR, Adderall, and MAS treatment periods.

No subject had a potentially clinically important low (<35°C) or high (>39°C) temperature or a potentially clinically important increase (≥7%) in body weight.

In general, none of the potentially clinically important vital sign changes were judged to be clinically important in the context of subject safety by the Investigator.

Subject 1-406 had an AE of postural dizziness. An individual subject narrative of this AE can be found in Section 8.3.5.4.

8.5.3 Electrocardiogram

Electrocardiogram measurements were to be performed at Screening, Check-in for each treatment period, prior to study drug dosing, and at 0.75, 1.5, 2.25, 3, 3.75, 4.5, 5.25, 6, 7.5, 9, 10.5, 12, 24, 48, and 60 hours following study drug dosing. Electrocardiograms were initially reviewed by the Investigator then sent to eResearch Technology for evaluation by a certified cardiologist. The ECG parameters and normal/abnormal assessments were transferred back to the study site. Any ECG considered abnormal by the cardiologist required further assessment of clinical significance by the Investigator.

8.5.3.1 ECGs over time

A summary of ECGs for subjects in the Safety population is provided in Section 12.1, Table 3.10. Individual subject ECG results are presented in Appendix 2, Listing 2.13. A summary of mean change from Baseline in QTcB, QTcF, and HR is presented in Table 22, Table 23, and Table 24, respectively. No clinically important trends in mean change from Baseline were noted for PR, QRS, QT, QTcB, QTcF, or HR during the Adderall XR, Adderall, or MAS treatment periods.

During the study, changes in QTcB and correlating increases in HR were observed. These observations are consistent with those in previous studies with Adderall XR. Because of the consistent increases in HR, the QTcF correction is more appropriate. Mean QTcF changes from Baseline are presented in Table 23.

Table 22: Mean (SD) Change from Baseline in QTcB Interval (msec) – Safety Population

	Adderall XR (N=18)	Adderall (N=17)	MAS (N=17)
Mean Baseline	398.6 (23.86)	401.4 (23.96)	404.9 (22.03)
0.75 hours postdose	5.7 (16.20)	10.2 (17.47)	8.1 (16.14)
1.5 hours postdose	19.1 (29.17)	14.4 (23.29)	8.0 (19.94)
2.25 hours postdose	13.7 (20.70)	9.2 (15.81)	10.7 (19.78)
3 hours postdose	13.3 (13.54)	9.6 (18.67)	4.5 (16.29)
3.75 hours postdose	11.5 (13.04)	9.3 (24.33)	8.5 (22.61)
4.5 hours postdose	17.1 (17.49)	9.9 (14.41)	7.8 (14.16)
5.25 hours postdose	20.6 (16.80)	13.6 (17.34)	10.7 (17.40)
6 hours postdose	15.8 (18.55)	18.1 (18.48)	8.2 (24.82)
7.5 hours postdose	12.4 (20.40)	7.9 (25.56)	6.8 (20.16)
9 hours postdose	11.9 (15.56)	10.6 (23.80)	6.9 (18.18)
10.5 hours postdose	17.9 (13.39)	10.8 (26.87)	11.1 (16.53)
12 hours postdose	13.4 (21.50)	8.0 (22.09)	7.8 (18.42)
24 hours postdose	14.8 (19.01)	18.1 (28.44)	13.5 (19.79)
48 hours postdose	8.6 (22.02)	12.7 (20.78)	8.9 (28.20)
60 hours postdose	7.8 (17.44)	15.0 (27.23)	9.2 (24.15)

Source: Section 12.1, Table 3.10

Table 23: Mean (SD) Change from Baseline in QTcF Interval (msec) – Safety Population

	Adderall XR (N=18)	Adderall (N=17)	MAS (N=17)
Mean Baseline	400.3 (16.94)	402.8 (16.23)	406.2 (16.35)
0.75 hours postdose	0.3 (12.00)	6.5 (11.44)	6.2 (13.42)
1.5 hours postdose	10.0 (21.35)	9.0 (13.73)	4.8 (13.01)
2.25 hours postdose	6.4 (13.04)	4.3 (10.23)	4.8 (14.28)
3 hours postdose	6.8 (11.89)	4.4 (13.57)	0.3 (11.65)
3.75 hours postdose	3.3 (10.28)	1.8 (17.81)	2.4 (15.79)
4.5 hours postdose	5.3 (11.86)	2.4 (11.01)	-0.7 (12.62)
5.25 hours postdose	-0.2 (12.30)	-3.1 (13.83)	-4.9 (14.42)
6 hours postdose	-3.2 (14.37)	-2.2 (15.57)	-7.8 (18.91)
7.5 hours postdose	-2.1 (14.59)	-5.8 (17.99)	-8.9 (18.59)
9 hours postdose	-1.2 (12.89)	-1.6 (18.24)	-5.3 (16.19)
10.5 hours postdose	-3.8 (12.82)	-7.0 (19.61)	-8.4 (11.84)
12 hours postdose	-4.7 (18.05)	-9.2 (13.79)	-7.9 (13.33)
24 hours postdose	3.9 (16.99)	5.1 (19.54)	3.7 (17.50)
48 hours postdose	1.3 (13.15)	3.8 (14.96)	1.7 (16.32)
60 hours postdose	-4.8 (10.77)	1.4 (15.23)	-4.2 (18.59)

Source: Section 12.1, Table 3.10

Table 24: Mean (SD) Change from Baseline in Heart Rate (bpm) – Safety Population

	Adderall XR (N=18)	Adderall (N=17)	MAS (N=17)
Mean Baseline	59.4 (12.65)	59.5 (11.42)	60.1 (13.71)
0.75 hours postdose	4.7 (7.48)	3.1 (9.06)	1.5 (7.61)
1.5 hours postdose	8.3 (9.43)	4.9 (14.14)	2.3 (8.54)
2.25 hours postdose	6.0 (10.95)	4.1 (8.80)	5.1 (9.15)
3 hours postdose	5.9 (7.97)	4.5 (8.43)	3.3 (8.45)
3.75 hours postdose	7.1 (9.89)	7.0 (11.35)	5.1 (9.62)
4.5 hours postdose	11.1 (11.86)	6.9 (10.46)	7.3 (10.44)
5.25 hours postdose	20.7 (14.14)	16.3 (11.83)	14.7 (10.89)
6 hours postdose	18.7 (12.15)	20.8 (13.88)	14.9 (12.50)
7.5 hours postdose	13.4 (12.44)	13.1 (14.45)	15.2 (10.21)
9 hours postdose	12.6 (10.15)	11.6 (9.96)	11.5 (15.77)
10.5 hours postdose	21.5 (9.51)	17.6 (9.29)	19.3 (12.30)
12 hours postdose	17.4 (8.77)	17.5 (12.88)	15.1 (11.19)
24 hours postdose	10.1 (6.80)	11.9 (9.34)	8.7 (5.46)
48 hours postdose	6.8 (11.11)	8.1 (9.77)	6.4 (13.24)
60 hours postdose	12.4 (10.58)	12.9 (14.30)	12.8 (9.88)

Source: Section 12.1, Table 3.10

8.5.3.2 Individual subject ECG changes

A summary of potentially clinically important ECG outliers is presented in Section 12.1, Table 3.11. Individual subject ECG results are presented in Appendix 2, Listing 2.13.

The number of subjects with a postdose QT interval ≥450msec and <480msec was generally similar to the number of subjects with a similar QT interval at the predose ECG assessment. One subject had QT interval ≥480msec during the study. Subject 1-414 had a QT interval of 493msec at 0.75 hours after receiving MAS. The subject's predose QT interval was 477msec. All QT interval values after the single high value were less than or the same as predose values. No subject had a QT interval ≥500msec during the study.

A summary of potentially clinically important QTcB outliers based on the criteria in Table 10 is presented in Table 25. The number of subjects with a QTcB interval outlier ≥450msec and <480msec was generally similar during the Adderall XR, Adderall and MAS treatment periods. There did not appear to be a pattern to the occurrence of QTcB outliers. One subject each during the Adderall and MAS treatment periods had a QTcB interval ≥480msec and

<500msec, one at 60 hours postdose and the other at 48 hours postdose, respectively. One subject had a QTcB interval ≥500msec. Subject 1-414 had a QTcB interval of 516msec 1.5 hours after receiving Adderall XR. The subject's predose QTcB interval was 402msec. All QTcB interval values after the single high value were ≤470msec.

Two subjects had a postdose QTcF interval ≥450msec and <480msec. Subject 1-414 had QTcF intervals of 456msec and 450msec at 2.25 and 24 hours after Adderall XR, respectively. This subject also had a QTcF interval of 458msec 48 hours after receiving MAS. Subject 1-422 had QTcF intervals of 450msec and 452msec at 0.75 and 3.0 hours after Adderall XR, respectively. This subject also had a QTcF interval of 451msec 2.25 hours after receiving Adderall. One subject had a QTcF interval ≥480msec and <500msec. Subject 1-414 had a QTcF interval of 499msec 1.5 hours after receiving Adderall XR. No subject had a QTcF interval ≥500msec.

Table 25: Summary of Potentially Clinically Important QTcB Outliers – Safety Population

	Adderall XR (N=18)			Adderall (N=17)			MAS (N=17)		
Time postdose	≥450 to <480	≥480 to <500	≥500	≥450 to <480	≥480 to <500	≥500	≥450 to <480	≥480 to <500	≥500
Predose	1	0	0	1	0	0	0	0	0
0.75	1	0	0	0	0	0	2	0	0
1.5	0	0	1	1	0	0	0	0	0
2.25	2	0	0	2	0	0	1	0	0
3.0	1	0	0	0	0	0	0	0	0
3.75	0	0	0	1	0	0	0	0	0
4.5	0	0	0	1	0	0	0	0	0
5.25	1	0	0	0	0	0	0	0	0
6.0	1	0	0	2	0	0	1	0	0
7.5	0	0	0	0	0	0	1	0	0
9.0	0	0	0	1	0	0	0	0	0
10.5	1	0	0	1	0	0	0	0	0
12	0	0	0	0	0	0	0	0	0
24	2	0	0	1	0	0	1	0	0
48	1	0	0	1	0	0	1	1	0
60	1	0	0	0	1	0	2	0	0

Source: Section 12.1, Table 3.11

Five subjects had a QTcB interval change ≥60msec from Baseline. A summary of these subjects is provided in Table 26.

Table 26: Summary of Subjects with a QTcB Interval Change of ≥60msec from Baseline

Subject ID	Treatment Period	Predose QTcB (msec)	Timepoint Postdose	QTcB Interval (msec)
1-406	Adderall XR	376	4.5 hours	437
1-408	Adderall	401	24 hours	468
1-410	Adderall XR	370	7.5 hours	434
	MAS	365	10.5 hours	432
	MAS		24 hours	430
1-414	Adderall XR	402	1.5 hours	516
	Adderall XR		2.25 hours	469
	Adderall	398	1.5 hours	472
	Adderall		60 hours	481
	MAS	404	48 hours	488
1-444	Adderall	378	24 hours	447

Source: Section 12.1, Table 3.11; Appendix 2, Listing 2.13

One subject had a QTcF interval change ≥60msec from Baseline. Subject 1-414 had a Baseline QTcF interval of 419msec and at 1.75 hours postdose the QTcF interval was 499msec, a change from Baseline of 90msec following Adderall XR administration.

Subject 1-414 had a change on ECG reported as an AE. An individual subject narrative of this AE can be found in Section 8.3.5.4.

Subject 1-419 was discontinued from the study due to ECG ST-T segment abnormalities. An individual subject narrative of this AE can be found in Section 8.3.5.3. This subject had two abnormal ECGs that were considered clinically significant by the Investigator. These abnormal findings were reported as AEs and the subject was dropped from the study. A subsequent over-read of the ECGs by a central reader, determined the ECGs to be normal. The information to support the Investigator's decision to withdraw the subject from the study is located on the AE and comments pages of the CRF. The ECG interpretation from the central reader is located on the ECG pages of the CRF.

8.5.4 Medical histories

Medical histories were collected from all subjects at the Screening Visit. Individual subject medical history data are presented in Appendix 2, Listing 2.4. A summary of the ongoing medical histories at study entry is presented in Table 27. Ten of the 18 subjects (55.6%) enrolled into the study had an ongoing medical history at study entry. None of the ongoing medical histories were clinically important.

As described in the study protocol, the Phase I unit was to request full medical histories from the subject's primary physician prior to enrollment into the study, if the subject had a primary physician and if the subject agreed to the primary physician being informed of the subject's participation in the study. The medical history for Subject 1-422 was not received from the subject's primary physician until after the third treatment period. At this time it was learned that the subject had a medical history of Muir-Torre syndrome with a cancer-related hysterectomy that, in the opinion of the Investigator, would have precluded her eligibility for the study had it been known at the time of Screening. Additionally, the subject had a history of irritable bowel syndrome, fibromyalgia, and depression. The Investigator felt that although individually these diagnoses would not have necessarily excluded the subject from the study, the combination of these conditions would have been strong grounds for exclusion.

Table 27: Ongoing Medical Histories at Study Entry – Safety Population

Subject ID	Body System	Diagnosis or Abnormality Description
1-443	HEENT	Lazy eye/strabismus
1-418	Other	Seasonal allergies
1-419	Other	Seasonal allergies
1-444	Other	Seasonal allergies
1-434	Other	Nonspecific seasonal allergies
1-421	Dermatologic	Vitiligo
1-405	HEENT Neurological Other Other	Intermittent stiff neck of musculoskeletal origin Headaches related to neck stress (infrequent) Allergic to cigarette smoke Seasonal allergies
1-414	Other	Allergic to poison ivy
1-408	Urogenital and Renal	Menstrual cramps
1-436	Other	Seasonal allergies

Source: Appendix 2, Listing 2.4

8.6 Safety Conclusions

- Adderall XR 30mg, Adderall 30mg, and MAS [5mg/mL] x 6mL were generally well-tolerated when administered as a single oral dose. There were no deaths or SAEs; the majority of TEAEs were considered to be mild, and all AEs resolved prior to subjects being discharge from the study.

- The percentage of subjects reporting a TEAE was generally similar during each Adderall XR (72.2%), Adderall (64.7%), and MAS (70.6%) treatment period.

- The most commonly reported TEAEs were contact dermatitis, palpitations, and dry mouth. All instances of contact dermatitis were confined to the chest and related to ECG lead placement. The percentage of subjects with treatment-emergent palpitations was higher during the MAS (17.6%) treatment period in comparison to during the Adderall XR

(11.1%) and Adderall (11.8%) treatment periods. The percentage of subjects with treatment-emergent dry mouth was higher during the Adderall (11.8%) and MAS (11.8%) treatment periods in comparison to during the Adderall XR (5.6%) treatment period.

- The most commonly reported TEAEs that were considered as having a suspected relationship to study drug were palpitations, dry mouth, hypervigilance, and vision blurred. All TEAEs of palpitations, dry mouth, hypervigilance, and vision blurred were considered by the Investigator as having a suspected relationship to study drug. The percentage of subjects with treatment-emergent palpitations was higher during the MAS (17.6%) treatment period in comparison to the Adderall XR (11.1%) and Adderall (11.8%) treatment periods. The percentage of subjects with treatment-emergent dry mouth was higher during the Adderall (11.8%) and MAS (11.8%) treatment periods in comparison to the Adderall XR (5.6%) treatment period. The percentage of subjects with treatment-emergent hypervigilance was higher during the MAS (17.6%) treatment period in comparison to the Adderall XR (0.0%) and Adderall (5.9%) treatment periods. The percentage of subjects with treatment-emergent vision blurred was higher during the Adderall XR (11.1%) treatment period in comparison to the Adderall (0.0%) and MAS (5.9%) treatment periods. All contact dermatitis AEs were not suspected to be related to study drug.

- There were no clinically significant treatment-emergent physical examination abnormalities or clinically significant treatment-emergent laboratory abnormalities.

- Mean systolic BP, diastolic BP, and HR increased after dosing during the Adderall XR, Adderall, and MAS treatment periods. These changes were not unexpected and did not lead to clinically important events.

- One subject had a transient prolongation of the QTc interval reported as an AE, however the event was considered by the Investigator as not suspected to be related to study drug. Another subject was discontinued from the study due to ECG ST-T segment abnormalities that were considered clinically significant by the Investigator upon initial review. A subsequent over-read of the ECGs for this subject by a central reader determined the ECGs to be normal.

9. DISCUSSION

This study was designed to assess the relative bioavailability of single 30mg doses of Adderall XR capsules and Adderall tablets vs. an oral solution of MAS [5mg/mL] x 6mL.

Statistical analyses between PK parameters obtained from healthy subjects receiving either Adderall XR, Adderall or MAS indicated that the exposure to both *d*- and *l*-amphetamine after a single dose of either Adderall XR or Adderall is comparable to the exposure after an oral dose of MAS solution.

No differences were observed between the elimination half-lives of either *d*-amphetamine or *l*-amphetamine following any of the three formulations tested. Furthermore, Vz/F, CL/F and their respective body weight normalized values were comparable between the treatments indicating that oral dose of either Adderall XR or Adderall would not alter the distribution and clearance of *d*- and *l*-enantiomers and will be equivalent to those following MAS reference treatment.

The median time to peak plasma concentrations for both enantiomers was approximately 2 hours later in subjects receiving Adderall XR when compared with MAS dose; however the T_{max} after Adderall and MAS doses were comparable. This delay in T_{max} after Adderall XR dose can be attributed to the extended release characteristic of the formulation.

A secondary objective of this study was to describe the safety profile of single 30mg doses of Adderall XR capsules, Adderall tablets, and an oral solution of MAS [5mg/mL]. The most commonly reported TEAEs with a suspected relationship to study drug were palpitations, dry mouth, hypervigilance, and vision blurred. These AEs were not unexpected and are commonly seen with amphetamine use[26].

Mean HR, SBP, and DBP increased after dosing during each Adderall XR, Adderall, and MAS treatment period. These changes are commonly seen with amphetamine use[26].

The safety findings from this study show that Adderall XR 30mg, Adderall 30mg, and MAS [5mg/mL] x 6mL were generally well-tolerated when administered as a single oral dose.

10. OVERALL CONCLUSIONS

The results from this study indicate that *d*- and *l*-amphetamine bioavailability after a dose of either Adderall XR or Adderall is comparable to the bioavailability of these enantiomers following a MAS dose.

Adderall XR 30mg, Adderall 30mg, and MAS [5mg/mL] x 6mL were generally well tolerated when administered as a single oral dose.

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