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RESEARCH**

APPLICATION NUMBER:

21-977

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

DRUG: Lisdexamfetamine

PRIMARY REVIEWER: Andre Jackson

NDA: 21977

TYPE: NDA

FORMULATION: Oral Capsule

STRENGTH: 30 MG, 50 MG AND 70
MG Capsules

APPLICANT: New River Pharmaceuticals

Submission Date:

December 22 , 2006

INDICATIONS: Attention Deficit Hyperactivity Disorder

REVIEW OF A RESPONSE TO AN APPROVABLE LETTER

The comments are related to dissolution and changes in the label by the firm.

Background:

The sponsor has stated that they can not meet the specification of \square % in 15 min and are proposing \square % in 20 min. The firm has also stated that on occasion they have to go to the S2 level i.e., an additional 6 units (average of 12 units is equal to or greater than Q, and no unit is less than Q-- \square %) to meet the \square % in 15 min specification.

Dissolution data has been supplied by the firm detailing dissolution for their 30 mg , 50 mg, and 70 mg capsules over an \square month period at 25 C and 60% relative humidity. The initial (0 month) release date data was collected for an N=12 whereas N=6 data was collected for months \square .

DISSOLUTION RESULTS:

\square BATCHES

30 mg

Dissolution Profile of NRP104 Packaged Batch 3043139 (25°C/60% RH)

Test / (Method)	Specification	Release							
Dissolution, Profile @ 15 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		92.1 (Avg) 6.2 (RSD)	85.9 (Avg) 6.5 (RSD)	91.2 (Avg) 4.4 (RSD)	95.3 (Avg) 4.8 (RSD)	89.0 (Avg) 6.4 (RSD)	89.2 (Avg) 9.7 (RSD)		
Dissolution, Profile @ 20 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		94.8 (Avg) 4.6 (RSD)	91.5 (Avg) 5.9 (RSD)	96.7 (Avg) 2.5 (RSD)	97.6 (Avg) 3.0 (RSD)	93.2 (Avg) 3.9 (RSD)	93.3 (Avg) 6.6 (RSD)		

50 mg

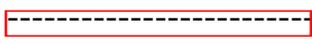
Dissolution Profile of NRP104 Packaged Batch 3043140 (25°C/60% RH)

Test / (Method)	Specification	Release							
Dissolution. Profile @ 15 Min	Record	[REDACTED]	[REDACTED]	96.6 (Avg) 3.6 (RSD)	97.4 (Avg) 4.2	95.3 (Avg) 7.0	97.8 (Avg) 2.1 (RSD)	96.2 (Avg) 4.9 (RSD)	101.3 (Avg) 1.0 (RSD)
Dissolution. Profile @ 20 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
				98.8 (Avg) 2.2 (RSD)	100.1 (Avg) 2.6 (RSD)	98.5 (Avg) 4.3 (RSD)	100.4 (Avg) 1.1 (RSD)	100.9 (Avg) 2.2 (RSD)	101.9 (Avg) 0.8 (RSD)

70 mg

Dissolution Profile of NRP104 Packaged Batch 3043141 (25°C/60% RH)

Test / (Method)	Specification	Release						
Dissolution, Profile @ 15 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		96.8 (Avg) 5.3 (RSD)	96.4 (Avg) 7.4 (RSD)	98.7 (Avg) 5.9 (RSD)	101.3 (Avg) 0.6 (RSD)	101.4 (Avg) 0.9 (RSD)	101.3 (Avg) 2.1 (RSD)	
Dissolution, Profile @ 20 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		99.2 (Avg) 2.9 (RSD)	98.9 (Avg) 5.1 (RSD)	100.3 (Avg) 4.3 (RSD)	101.4 (Avg) 0.5 (RSD)	101.8 (Avg) 1.0 (RSD)	103.2 (Avg) 0.8 (RSD)	

 BATCHES

30 MG

LISSOLUTION PROFILE OF NRP104 PACKAGED BATCH 3045507 (25°C/60% RH)

Test / (Method)	Specification	Release					
Dissolution, Profile @ 15 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		101.0 (Avg) 2.2 (RSD)	99.0 (Avg) 2.8 (RSD)	83.7 (Avg) 9.0 (RSD)	92.6 (Avg) 10.2 (RSD)	97.1 (Avg) 6.0 (RSD)	
Dissolution, Profile @ 20 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		101.8 (Avg) 1.5 (RSD)	101.0 (Avg) 1.6 (RSD)	91.7 (Avg) 5.2 (RSD)	99.7 (Avg) 4.7 (RSD)	99.8 (Avg) 3.7 (RSD)	

70 MG

Dissolution Profile of NRP104 Packaged Batch 3045931 (25°C/60% RH)

Test / (Method)	Specification	Release						
Dissolution, Profile @ 15 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		99.3 (Avg) 5.4 (RSD)	98.5 (Avg) 4.5 (RSD)	98.6 (Avg) 5.8 (RSD)	98.4 (Avg) 3.4 (RSD)	102.7 (Avg) 3.0 (RSD)		
Dissolution, Profile @ 20 Min	Record	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]	[REDACTED]
		101.8 (Avg) 3.0 (RSD)	100.9 (Avg) 2.2 (RSD)	99.8 (Avg) 4.4 (RSD)	99.3 (Avg) 3.6 (RSD)	102.6 (Avg) 3.2 (RSD)		

Comments:

1. DISSOLUTION

a. The dissolution data presented by the firm indicates that up to $\frac{1}{2}$ mos most of the dissolution data meets the S1 specification of each unit not less than $Q_{\frac{1}{2}}$ %. This would strongly support all strengths meeting the specification for S2 in which is no unit is less than $Q_{\frac{1}{2}}$ %.

b. Conducting dissolution at the S2 level is acceptable to OCP.

The sponsor is requested to adopt the following final specification for all strengths:

Final dissolution method and specification for all 3 capsule strengths is:

USP Apparatus 2 (paddle)
50 RPM
900 ml of 0.1 N ---L
Specification: $Q_{\frac{1}{2}}$ % in 15 minutes

2. LABEL

The firm has accepted all of the OCP proposed changes to the label.

SIGNATURES

Andre Jackson _____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology

RD/FTinitialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 21-977, HFD-860(Mehta, Baweja, Jackson)

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/s/

Andre Jackson
1/30/2007 09:08:00 AM
BIOPHARMACEUTICS

Raman Baweja
1/30/2007 04:40:46 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIPHARMACEUTICS REVIEW

DRUG: Lisdexamfetamine

PRIMARY REVIEWER: Andre Jackson

NDA: 21977

TYPE: NDA

FORMULATION: Oral Capsule

STRENGTH: 30 MG, 50 MG AND 70
MG Capsules

APPLICANT: New River Pharmaceuticals

Submission Date:

October 24, 2006

INDICATIONS: Attention Deficit Hyperactivity Disorder

REVIEW OF AN APPROVABLE LETTER

The comments are related to dissolution and changes in the label by the firm.

1. DISSOLUTION

FDA Comments:

- The sponsor has stated that they can meet the specification of $\geq 85\%$ in 15 min
- The firm has also stated that on occasion they have to go to the S2 level i.e., an additional 6 units (average of 12 units is equal to or greater than Q, and no unit is less than $Q_{\geq 85\%}$).
- The S2 level is acceptable to OCP
- The sponsor is requested to adopt the following final specifications for all strengths:

Final dissolution method and specification for all 3 capsule strengths is:

USP Apparatus 2 (paddle)

50 RPM

900 ml of 0.1 N HCL

Specification: $Q_{\geq 85\%}$ in 15 minutes

2. LABEL

Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology

RD/FTinitialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology
cc: NDA 21-977, HFD-860(Mehta, Baweja, Jackson)

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this page is the manifestation of the electronic signature.**

/s/

Andre Jackson
11/21/2006 02:02:12 PM
BIOPHARMACEUTICS

Raman Baweja
11/21/2006 02:40:11 PM
BIOPHARMACEUTICS

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS REVIEW

DRUG: Lisdexamfetamine

PRIMARY REVIEWER: Andre Jackson

NDA: 21977

TYPE: NDA

FORMULATION: Oral Capsule

STRENGTH: 30 MG, 50 MG AND 70
MG Capsules

APPLICANT: New River Pharmaceuticals

Submission Date:

December 6, 2005

INDICATIONS: Attention Deficit Hyperactivity Disorder

EXECUTIVE SUMMARY:

The Sponsor's objective is to develop a drug treatment for ADHD with reduced abuse potential compared to other Schedule II substances used in similar medical situations. The active ingredient in NRP 104 capsules is lisdexamfetamine as the dimesylate salt, a new chemical entity. Lisdexamfetamine, like diethylpropion (a Schedule IV stimulant), depends on biotransformation to exert its pharmacological effect. In its intact form lisdexamfetamine dimesylate lacks stimulant properties and is pharmacologically inactive. When taken orally, the amide linkage is hydrolyzed in the gastrointestinal tract, releasing active d-amphetamine. Also like diethylpropion, there is limited biotransformation of lisdexamfetamine when administered via parenteral routes of administration. The Sponsor believes, based on results to date, that lisdexamfetamine has substantially reduced abuse liability compared to d-amphetamine and other Schedule II stimulants.

The following studies were requested by FDA from the firm to support their Clinical data.

- an assessment of relative bioavailability to the optimally available oral formulation;
- a pediatric PK study that should be performed prior to phase III studies in order to aid in the selection of dosages for the pivotal phase III studies;
- a metabolism and mass balance study;
- a study to examine the effects of extrinsic factors such as food;
- use of literature sources and *in vitro* data to address drug-drug interactions; and
- complete dissolution profile data in 3 media and under various conditions.

The firm has conducted the following studies to support their NDA:

1. Study No. NRP 104.101

A Pharmacokinetic Study to Assess the Rate of Absorption and the Oral Bioavailability of Two Dose Levels of NRP104 Capsules to Doses of the Reference Products, Dexedrine Spansules and Adderall XR Capsules Under Fasting Conditions

2. Study No. NRP 104.102

A Single-Dose, 3-Treatment, 3-period, Crossover Pharmacokinetic Study to Assess Relative Bioavailability of NRP104 70 mg Capsules (1x70 mg) Under Fed State and Solution vs. Fasted State in Healthy Adult Volunteers

3. Study No. NRP 104.103

A Single-Dose, 3 Treatment, 3-period, Crossover Pharmacokinetic Study to Assess Dose Proportionality of NRP 104 30 mg Capsules (1x30mg), 50 mg Capsules (1x50mg), and 70 mg Capsules (1x70mg) in Children Aged 6-12 years with ADHD.

4. Study No. NRP 104.104

A Multiple-Dose Single-Arm Pharmacokinetics Study of NRP104 70 mg Capsules (1 x 70 mg) Following 7-Day Administration in Healthy Adult Volunteers Under Fasting Condition

Geometric mean comparison between 75mg-NRP104 (22.2 mg d-amphetamine) and 30mg-Dexedrine (22.0 mg d-amphetamine) indicated comparable extents of d-amphetamine exposure but a 48% higher C_{max} for NRP104. On the other hand, d-amphetamine exposure for extent and C_{max} from 75 mg NRP104 was comparable to (d+l) amphetamine from Adderall XR despite different molar amounts of the active moiety in the dosage form (i.e., and 22.2 mg d-amphetamine for NRP104 and 16.6 mg d-amphetamine-Adderall XR).

The results from the food effect study showed that the intact NRP104 C_{max} and AUC_{inf} levels were decreased by food 45% and 12% respectively, but there was no effect on d-amphetamine C_{max} or AUC_{inf} values. These results are not unexpected since the parent drug, intact NRP104, would be expected to be more variable than the metabolite, d-amphetamine. The capsule and oral solution formulations of NRP104 were equally bioavailable.

Based on the results of both a dose-normalized bioequivalence approach and a power model, it has been shown that d-amphetamine (AUC and C_{max}) were dose proportional in the range from 30 mg to 70 mg NRP104, when given as a single dose to children aged 6-12 years with ADHD. Dose normalized exposures of d-amphetamine are comparable between boys and girls. Unlike d-amphetamine, intact NRP104 did not show dose proportionality in the dose range of 30 mg to 70 mg NRP104. A mass balance study showed that 96% of the drug is excreted in the urine as metabolites . D-Amphetamine and hippuric acid were the major metabolites in 0 to 48h urine samples.

The capsule and oral solution have comparable bioavailability. Metabolite AUC levels (i.e., d-amphetamine) are 16x higher than for the parent pro-drug NRP-104.

In healthy adults multiple dose pharmacokinetics following a 70 mg daily dose for 7 days showed no accumulation of NRP104. Steady-state for d-

amphetamine was reached in 5 days. Dose normalized Day 7 d-amphetamine AUCinf and Cmax values were 22% and 12% lower in women than in men.

Dissolution in all media was very rapid (-----% dissolved in 10 minutes) using Apparatus 2, paddle at 50 rpm). Dissolution In 0.1N HCL was the slowest (i.e., -----% in 15 min).

COMMENT TO THE SPONSOR

Final dissolution method and specifications for all 3 capsule strengths is:

USP Apparatus 2 (paddle)

50 RPM

900 ml of 0.1 N HC-

Specification: Q=-----% in 15 minutes

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QUESTION BASED REVIEW

WHAT IS THE COMPOSITION OF THE LISDEXAMPHETAMINE DOSAGE FORM AND HOW DO THE D-AMPHETAMINE MOIETY COMPARE TO ADDERALL XR AND DEXEDRINE?

NRP104 (L-lysine *d*-amphetamine dimesylate) is a pro-drug of *d*-amphetamine. The proposed commercial formulation of NRP104 is a capsule containing 30 mg, 50 mg, or 70 mg of the pro-drug; the content expressed as *d*-amphetamine sulfate and *d*-amphetamine. However, the pharmacokinetic data were collected using a 25 mg and 75 mg capsule.

CONTENT of NRP104 CAPSULES DEXEDRINE, AND ADDERALL XR, EXPRESSED AS THE D AND L AMPHETAMINE BASE

Doses of the Four Treatments as Amphetamine Base

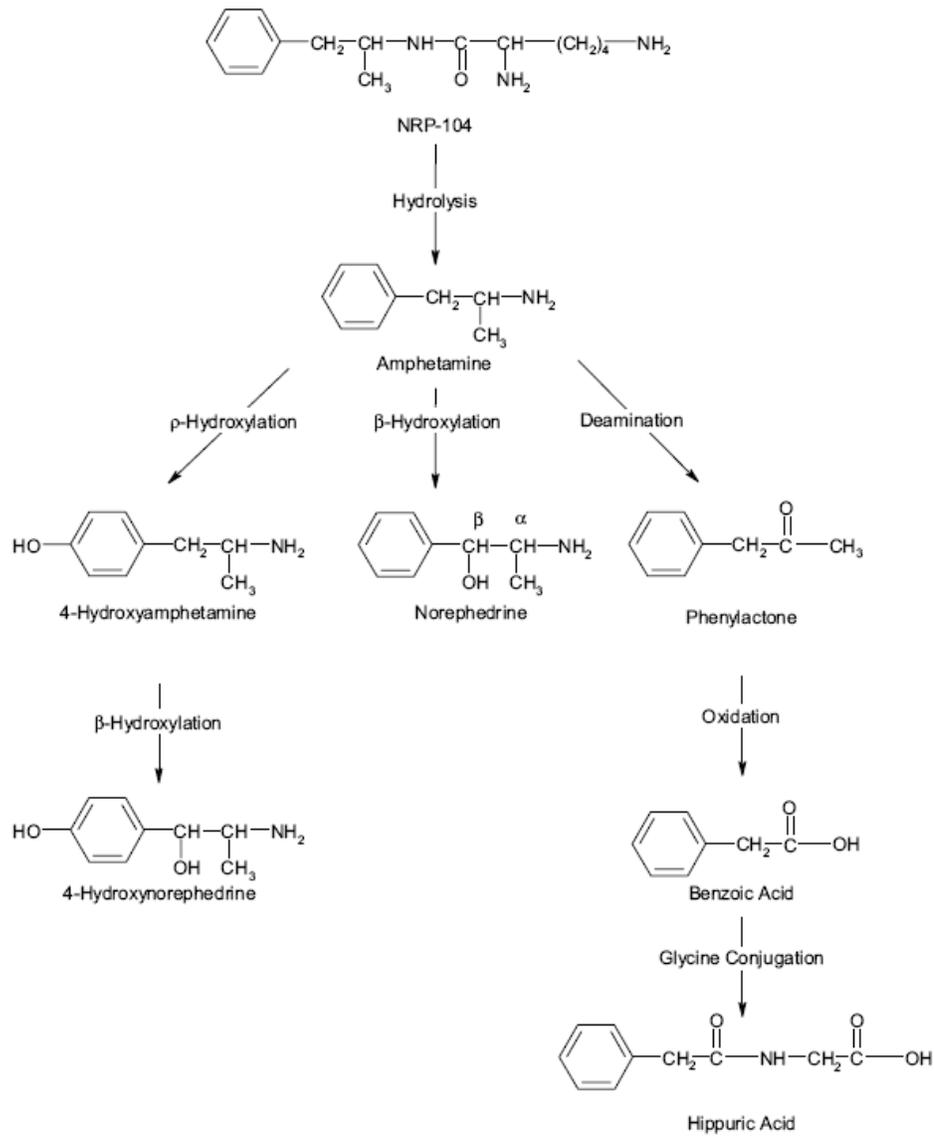
Formulation	Labeled dose (mg)	dose (mg) as:		
		d-amp	l-amp	total amp
NRP104	25	7.425	0	7.425
NRP104	75	22.275	0	22.275
Adderall XR	35	16.625	5.285	21.91
Dexedrine	30	22.02	0	22.02

Based on molecular weights of 455.59, 368.49, and 135.20 for lysine-amphetamine, *d*-amphetamine sulfate, and *d*-amphetamine, respectively.

The apparent differences in the amount of d-amphetamine between Adderall XR 35 mg and NRP104 75 mg 7.425 mg. However, this difference will have to be addressed by the Medical Officer to determine if it is of Clinical Significance.

WHAT IS THE PROPOSED METABOLIC SCHEME FOR LISDEXAMPHETAMINE?

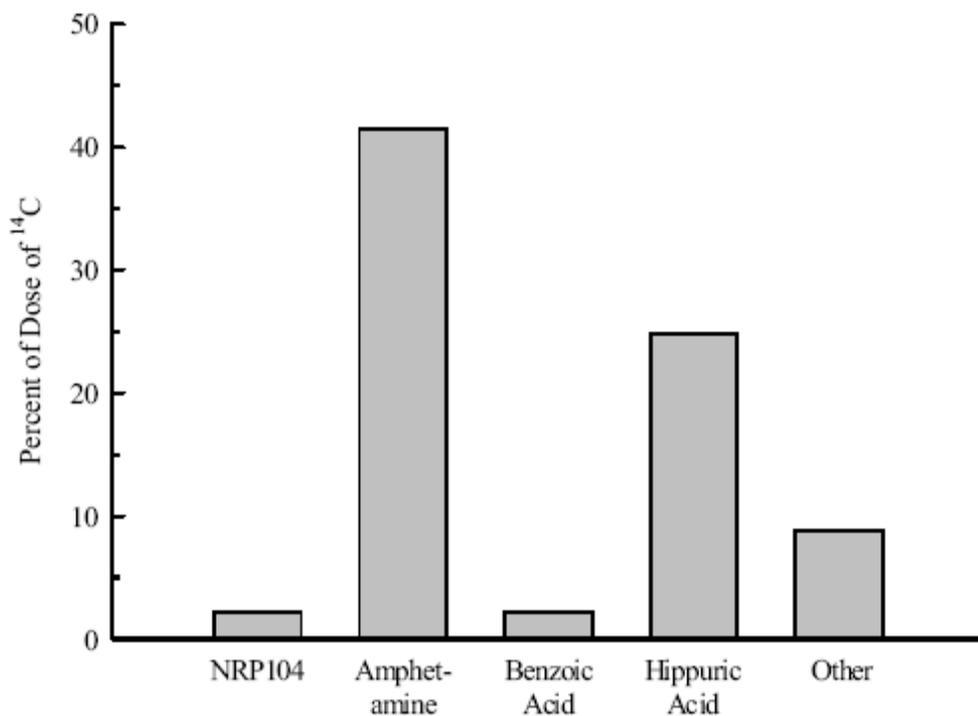
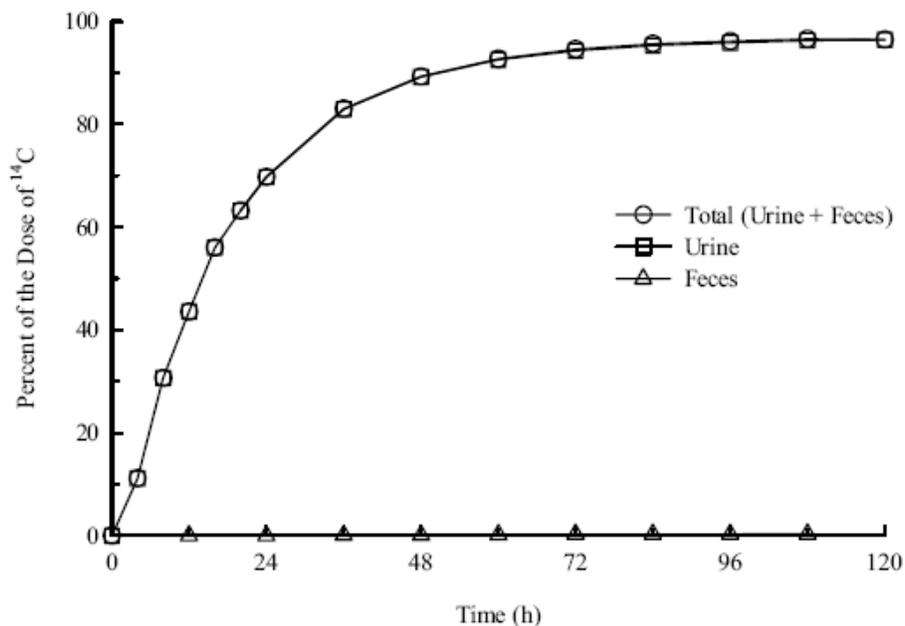
Figure 2.7.2-4 Proposed Metabolic Scheme for NRP104



WHAT ARE THE MAJOR ROUTES OF ELIMINATION FOR LISDEXAMPHETAMINE?

Figure 2.7.2-2

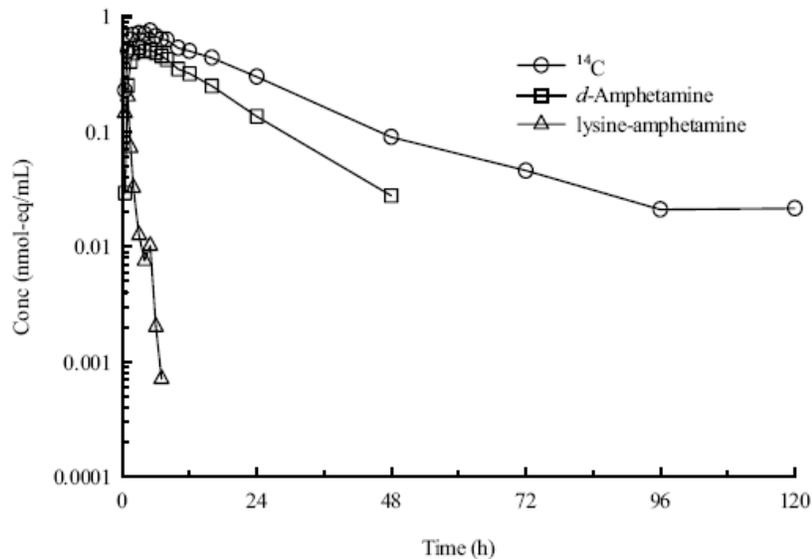
Mean Cumulative Urinary and Fecal Excretion of Total ^{14}C after Oral Administration of a 70 mg Doses of ^{14}C -NRP104 under Fasted Conditions to Healthy Volunteers



Renal elimination is the major route of excretion.

WHAT IS THE MAJOR SPECIES OBSERVED IN THE PLASMA FOLLOWING LISDEXAMPHETAMINE ADMINISTRATION?

Figure 2.7.2-1 Mean Plasma Concentrations of Total ¹⁴C, *d*-amphetamine Base, and NRP104 after Oral Administration of a 70 mg Doses of ¹⁴C-NRP104 under Fasted Conditions to Healthy Volunteers



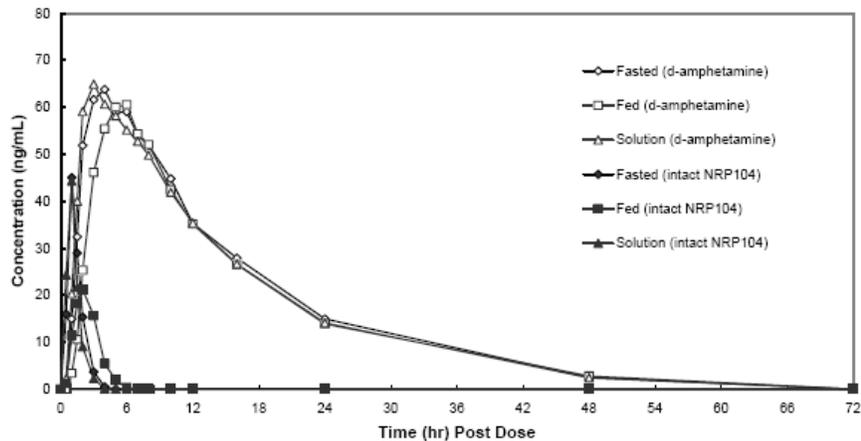
The major metabolite in plasma is d-amphetamine.

IS THE RELATIVE BIOAVAILABILITY OF NRP104 70 MG CAPSULES (1X70 MG) AFFECTED BY FOOD ?

A study done in 18 normal adults gave the following results.

**SUMMARY RESULTS
PHARMACOKINETICS:**

**Average Plasma Drug Concentration-Time Plot:
d-amphetamine and intact NRP104**



d-Amphetamine

	PK Parameters: Mean			
	AUC _(0-inf) (ng.hr/mL)	AUC _(0-t) (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
1x70 mg Fasted	1110	1020	69.3	3.78
1x70 mg Fed	1038	972	65.3	4.72 [^]
1x70 mg Solution	1074	1007	68.4	3.33
	Bioequivalence: % Ratio (90% CI)			
Fed/Fasted	95.93 (90.74, 101.41)*	97.51 (90.65, 104.90)*	94.26 (89.97, 98.75)*	
Solution/Fasted	99.40 (94.03, 105.09)*	101.27 (94.14, 108.94)*	98.57 (94.08, 103.27)*	

Intact NRP104

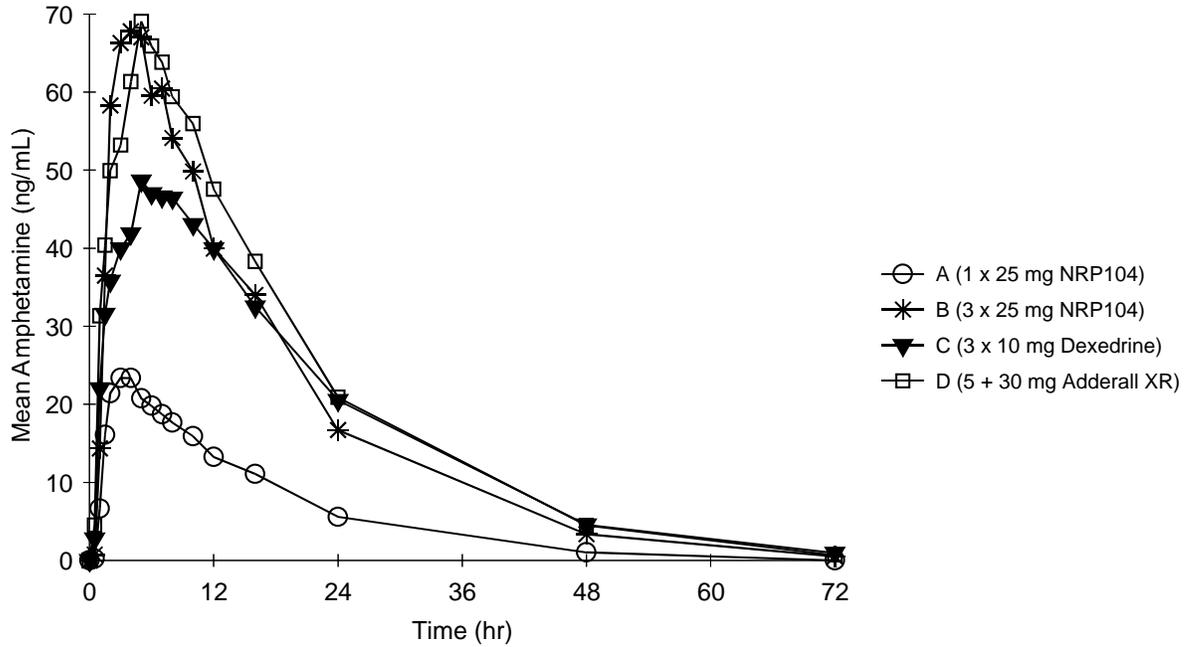
	PK Parameters: Mean			
	AUC _(0-inf) (ng.hr/mL)	AUC _(0-t) (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
1x70 mg Fasted	66.84	59.47	48.0	1.15
1x70 mg Fed	58.81	53.68	26.2 [^]	2.08 [^]
1x70 mg Solution	55.10	53.07	45.6	0.97
	Bioequivalence: % Ratio (90% CI)			
Fed/Fasted	86.66 (76.03, 98.79)	93.60 (81.73, 107.21)*	55.82 (47.03, 66.26)	
Solution/Fasted	85.52 (75.52, 96.85)	93.87 (81.96, 107.52)*	101.19 (85.25, 120.11)*	

[^] p<0.05 (Dunnett's test) compared to Fasted, following a statistically significant (p<0.05) overall treatment effect

* within the 80% to 125% bioequivalence limits

The results indicate that for the parent drug there is a decrease of 12% on AUC_{inf}, a 9% decrease on AUC_t and 45% decrease on C_{max} in the presence of food. There is no appreciable effect of food on the d-amphetamine metabolite which is expected since it is formed during the absorption process. Comparable AUC and C_{max} values were obtained for d-amphetamine from the capsule and solution formulation. Exposure of the metabolite d-amphetamine is 16 fold higher than that seen for the parent drug NRP-104.

WHAT IS THE RELATIVE BIOAVAILABILITY BETWEEN NRP104 CAPSULES AND THE REFERENCE PRODUCTS, DEXEDRINE AND ADDERALL XR



The resulting 90% confidence intervals were:

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-Amphetamine (Parallel Design for Comparing 75 mg NRP104 to Dexedrine)

Dependent Variable	Geometric Mean		Ratio (%) (Test/Reference)	90% Confidence Interval	
	Test	Reference		Lower	Upper
ln(C _{max})	73.0227	49.3560	147.95	128.49	170.36
ln(AUC _{last})	1223.5446	1174.2369	104.20	91.06	119.23
ln(AUC _{inf})	1246.5279	1197.4589	104.10	91.23	118.78

Statistical analysis of the log-transformed systemic exposure parameters of d amphetamine from NRP104 to the racemic mixture (d+ l-Amphetamine) from Adderall XR (Crossover design for comparing 75 mg NRP104 to 35 mg Adderall XR).

Dependent Variable	Geometric Mean		Ratio (%) (Test/Reference)	90% Confidence Interval	
	Test	Reference		Lower	Upper
ln(C _{max})	73.0227	72.3927	100.87	94.19	108.03
ln(AUC _{0-∞})	1223.5446	1387.5133	88.18	82.98	93.71
ln(AUC _{0-t})	1246.5279	1414.5184	88.12	83.85	92.62

Note: Comparisons to Adderall XR are based on total (d+l) amphetamine

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of d-Amphetamine (Crossover design for Comparing 25 mg NRP104 to Dexedrine after Dose-Normalization)

Dependent Variable	Geometric Mean		Ratio (%) (Test/Reference)	90% Confidence Interval	
	Test	Reference		Lower	Upper
ln(C _{max})	73.3243	49.3560	148.56	135.72	162.61
ln(AUC _{0-∞})	1159.3989	1174.2369	98.74	88.64	109.98
ln(AUC _{0-t})	1219.7728	1197.4589	101.86	92.24	112.49

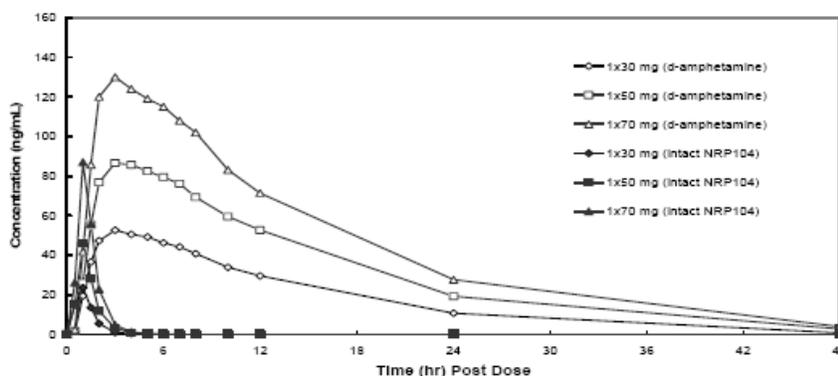
These results indicate that AUC and C_{max} for d-amphetamine from 75 mg NRP 104 were comparable to (d+l-amphetamine) from 35 mg Adderall XR. The data also show d-amphetamine equivalence for AUC for 75 mg NRP 104 and 30 mg Dexedrine while peak exposure was 48% higher from NRP104 than from Dexedrine.

ARE THE PHARMACOKINETICS OF LISDEXAMPHETAMINE LINEAR?

A study conducted in 18 children 6-12 yrs of age (10m/8F) gave the following results.

PHARMACOKINETICS:

**Average Plasma Drug Concentration-Time Plot:
d-amphetamine and Intact NRP104**



d-Amphetamine

PK Parameters: Mean

	AUC _(0-inf) (ng.hr/mL)	AUC _(0-t) (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
NRP104 1x30 mg	844.6	745.3	53.2	3.41
NRP104 1x50 mg	1510	1448	93.3	3.58
NRP104 1x70 mg	2157	2088	134	3.46

Bioequivalence (dose-normalized to 50 mg): % Ratio (90% CI)

30 mg to 50 mg	93.28 (87.36, 99.60)*	85.66 (79.12, 92.74)	95.25 (90.56, 100.17)*
70 mg to 50 mg	101.62 (95.34, 108.31)*	102.42 (94.80, 110.65)*	102.36 (97.46, 107.51)*

Power Model: P = a x Dose^b

b constant	1.1027	1.2191	1.0887
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Intact NRP104

PK Parameters: Mean (SD)

	AUC _(0-inf) (ng.hr/mL)	AUC _(0-t) (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
NRP104 1x30 mg	27.88	25.54	21.9	0.97
NRP104 1x50 mg	57.90	56.20	46.0	0.98
NRP104 1x70 mg	108.9	107.4	89.5	1.07

Bioequivalence (dose-normalized to 50 mg): % Ratio (90% CI)

30 mg to 50 mg	78.55 (69.16, 89.23)	74.83 (65.60, 85.36)	84.31 (69.57, 102.17)
70 mg to 50 mg	130.27 (115.08, 147.45)	132.96 (116.97, 151.12)	141.71 (117.55, 170.84)

Power Model: P = a x Dose^b

b constant	1.5452	1.6308	1.5826
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* within the 80% to 125% bioequivalence limits

The results show that the pharmacokinetics for the intact NRP104 exhibit nonlinear kinetics over the doses of 30-70 mg while the metabolite d-amphetamine exhibits dose proportional kinetics. The apparent higher exposures of d-amphetamine in girls compared to boys is not seen when normalized by mg/kg dose.

WHAT ARE THE STEADY-STATE KINETICS FOR D-AMPHETAMINE IN ADULTS?

A 70 mg daily dose for 7 days in 12 healthy adults (4M/8F) indicated that steady-

6 Page(s) Withheld

Trade Secret / Confidential



Draft Labeling

Deliberative Process

SIGNATURES

Andre Jackson _____
Reviewer, Psychopharmacological Drug Section, DCP I
Office of Clinical Pharmacology and Biopharmaceutics

RD/FTinitialized by Raman Baweja, Ph.D. _____

Team Leader, Psychiatry Drug Section, DCP I
Office of Clinical Pharmacology

cc: NDA 21-977, HFD-860(Mehta, Raman, Baweja, Jackson)

OCPB Briefing August 3, 2006

Briefing attendees list: Chandra Sahajwalla, Shiew-Mei Huang, Atik Rahman, Ken Thummel,
Nhi Khin, Tom Laughren, Gwen Zornberg, Mark Ritter, John Lazor, Michelle Chuen,
Mehul Mehta, Andre Jackson, Ray Baweja.

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STUDY DETAILS

A Single -Dose, 3-Treatment, 3-period, Crossover Pharamacokinetic Study to Assess Relative Bioavailability of NRP104 70 mg Capsules (1x70 mg) Under Fed State and Solution vs. Fasted State in Healthy Adult Volunteers Study No. 104.102

OBJECTIVES:

To assess relative bioavailability of *d*-amphetamine of NRP104 70 mg (1x70 mg) in healthy adult volunteers when administered orally either with food or in solution, compared to an intact capsule under fasted state.

PROTOCOL NO.; NRP104.102

METHODS

This was an open-label, single-dose, 3-treatment, 3-period, 6-sequence, randomized, crossover, Phase I bioavailability and bioequivalence study. A single NRP104 dose of 70 mg (1x70 mg) was administered to each subject under three dosing conditions: an intact capsule only, a solution containing the capsule contents, and an intact capsule with high fat meal. Prior to being dosed under these conditions, all subjects had an overnight fasting of at least 10 hours, and were fasted through at least 4 hours following drug administration.

The study enrolled eighteen (18) healthy adults aged 18 to 55 years.

Blood samples were determined for the plasma levels of *d*-amphetamine and intact NRP104 at the following hours: (dose time) 0 hour, and 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, and 72 hours postdose.

A standard clinic snack (approximately 11 hours prior to dose administration) was served the evening of check-in. All subjects were required to fast for at least ten (10) hours prior to dosing. Water was allowed *ad lib.* during the study, except for one (1) hour prior through two (2) hours post-dose.

Subjects receiving **Treatments A** and **C** did not receive breakfast.

Subjects receiving **Treatment B** received the following high fat breakfast within 30 minutes prior to dosing and must complete the meal within 5 minutes prior to dosing:

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

Treatments:

Treatment	Study Drug	Dose/Condition	Lot Number
A: Fasted	70 mg NRP104 capsules	1 x 70 mg capsule/ without food	3040830
B: Fed	70 mg NRP104 capsules	1 x 70 mg capsule/ with food	3040830
C : Solution	70 mg NRP104 capsules	1 x 70 mg capsule/ in solution	3040830

Pharmacokinetic Parameters:

From the plasma drug levels obtained from the study subjects, the following pharmacokinetic (PK) parameters (for both *d*-amphetamine and intact NRP104) were measured and calculated for bioavailability and bioequivalence evaluations at , , using non-compartmental methods and actual blood collection time intervals post dose:

- AUC_{0-t} : Area under the drug concentration-time curve from time zero to time t where t is the last timepoint with a drug concentration \geq LOQ (C_t).
- AUC_{0-inf} : Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + C_t/\lambda_z$, where λ_z is the terminal elimination rate constant.
- $t_{1/2}$: Elimination half-life calculated as $0.693/\lambda_z$.
- C_{max} : Maximum observed drug concentration.
- T_{max} : Time at which C_{max} occurs.

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

Characteristic	Category/Parameter	Total (N=18)
Race (%)	Caucasian	11 (61%)
	African American	2 (11%)
	Hispanic	4 (22%)
	Asian American	1 (6%)
Gender (%)	Male	9 (50%)
	Female	9 (50%)
Height (cm)	Mean	173.4
	SD	9.2
	Median	174.3
	Min-Max	159.5 – 191.0
Weight (kg)	Mean	70.4
	SD	10.3
	Median	68.1
	Min-Max	54.5 – 88.5
Age (years)	Mean	31.6
	SD	8.6
	Median	29.0
	Min-Max	18.0 – 46.0

Source: Section 15 Table 1.2.1

Analytical NRP104.102

Study NRP104.102

Subject(s)	Period	Dosing Date	Sample Analysis Date	# of Days Between Dosing and Analysis
1-4	1	12/2/2004	1/18/2005	47
1-4	2	12/9/2004	1/18/2005	40
1-4	3	12/16/2004	1/18/2005	33
5-12	1	12/2/2004	1/19/2005	48
5-12	2	12/9/2004	1/19/2005	41
5-12	3	12/16/2004	1/19/2005	34
13-18	1	12/2/2004	1/20/2005	49
13-18	2	12/9/2004	1/20/2005	42
13-18	3	12/16/2004	1/20/2005	35

Total Storage Period 33-48 days

Assay Validation

Parameter	Amphetamine 2-200 ng/ml	NRP-104 1-100 ng/ml
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection
Freeze- thaw	3 cycles	3 cycles
Benchtop Stability at RT	47 hrs	47 hrs
Long term at -20° C	21 days(6 and 160 ng/ml)	21 days(3 and 80 ng/ml)
Recovery Low High	44%	27%

Plasma Analysis Results

Study dates: November 12, 2004

December 28, 2004

Parameter	Amphetamine	NRP-104
Method	HPLC with Mass Spectrometric Detection	HPLC with Mass Spectrometric Detection
Sensitivity/LOQ	2 ng/ml	1 ng/ml
Linearity (Standard curve samples)	2-200 ng/ml	1-100 ng/ml
Quality Control (QC) Samples	6, 40 and 160 ng/ml	3, 20, 80 ng/ml
Precision of Standards (%CV)	2% @ 2 ng/ml 1.6% @ 200 ng/ml	2.9% @ 1 ng/ml 3.1% @ 100 ng/ml
Precision of QC Samples (%CV)	6.8% @ 6 ng/ml 5.4 % @ 160 ng/ml	6.1 % @ 3 ng/ml 12.9 % @ 80 ng/ml
Accuracy of Standards (%)	99.5% @ 2 ng/ml	100% @ 1 ng/ml

	100%@ 200 ng/ml	97%@ 100 ng/ml
Accuracy of QC Samples (%)	95.3 %@ 6 ng/ml 94.4 %@ 160 ng/ml	91 %@ 3 ng/ml 99 %@ 80 ng/ml

RESULTS

Table 2. Mean and S.D. of PK Parameters for *d*-amphetamine (PK Population)

PK parameters	Measures	NRP104 Fasted	NRP104 Fed	NRP104 Solution
AUC _{0-inf} (ng hr/mL)	N	18	17	17
	Mean	1110	1038	1074
	S.D.	314.2	238.6	220.8
AUC _{0-t} (ng hr/mL)	N	18	18	18
	Mean	1020	972	1007
	S.D.	319.8	228.3	223.5
C _{max} (ng/mL)	N	18	18	18
	Mean	69.3	65.3	68.4
	S.D.	14.3	13.4	14.6
T _{max} (hr)	N	18	18	18
	Mean [^]	3.78	4.72	3.33
	S.D.	1.01	1.07	1.19
t _{1/2} (hr)	N	18	17	17
	Mean	9.69	9.59	9.37
	S.D.	1.96	1.89	2.06

[^] Differences among the three treatments were highly significant (p<0.0001, ANOVA)

Source: Appendix Section 16.1.9.2.a, Pharmacokinetic and Bio-analytical Analysis Report, Pages 24, 26 and 27.

Table 3. Mean and S.D. of PK Parameters for Intact NRP104 (PK Population)

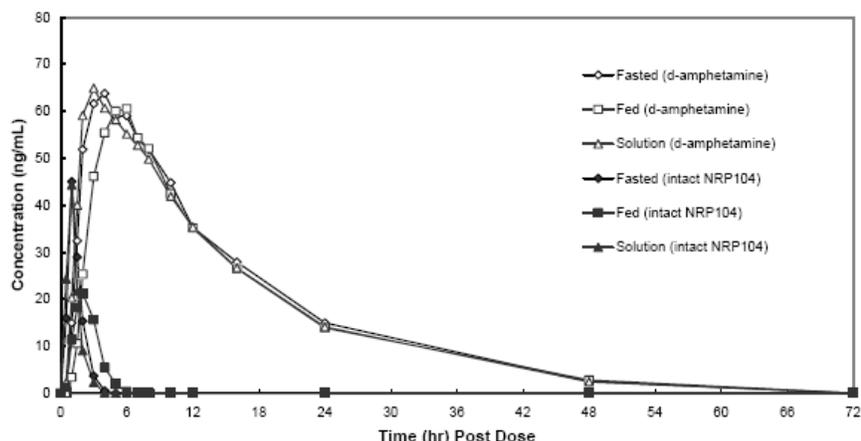
PK parameters	Measures	NRP104 Fasted	NRP104 Fed	NRP104 Solution
AUC _{0-inf} (ng hr/mL)	N	13	16	17
	Mean	66.84	58.81	55.10
	S.D.	23.61	15.26	16.97
AUC _{0-t} (ng hr/mL)	N	18	18	18
	Mean	59.47	53.68	53.07
	S.D.	24.85	17.72	16.56
C _{max} (ng/mL)	N	18	18	18
	Mean ^	48.0	26.2	45.6
	S.D.	23.8	11.9	17.0
T _{max} (hr)	N	18	18	18
	Mean ^	1.15	2.08	0.97
	S.D.	0.28	0.65	0.27
t _{1/2} (hr)	N	13	16	17
	Mean ^	0.41	0.63	0.44
	S.D.	0.07	0.20	0.10

^ Differences among the three treatments were highly significant (p<0.0001, ANOVA)

Source: Appendix Section 16.1.9.2.a, Pharmacokinetic and Bio-analytical Analysis Report, Pages 24, 28 and 29.

**SUMMARY RESULTS
PHARMACOKINETICS:**

**Average Plasma Drug Concentration-Time Plot:
d-amphetamine and intact NRP104**



d-Amphetamine

	PK Parameters: Mean			
	AUC _(0-inf) (ng.hr/mL)	AUC _(0-t) (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
1x70 mg Fasted	1110	1020	69.3	3.78
1x70 mg Fed	1038	972	65.3	4.72 [^]
1x70 mg Solution	1074	1007	68.4	3.33
	Bioequivalence: % Ratio (90% CI)			
Fed/Fasted	95.93 (90.74, 101.41)*	97.51 (90.65, 104.90)*	94.26 (89.97, 98.75)*	
Solution/Fasted	99.40 (94.03, 105.09)*	101.27 (94.14, 108.94)*	98.57 (94.08, 103.27)*	

Intact NRP104

	PK Parameters: Mean			
	AUC _(0-inf) (ng.hr/mL)	AUC _(0-t) (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
1x70 mg Fasted	66.84	59.47	48.0	1.15
1x70 mg Fed	58.81	53.68	26.2 [^]	2.08 [^]
1x70 mg Solution	55.10	53.07	45.6	0.97
	Bioequivalence: % Ratio (90% CI)			
Fed/Fasted	86.66 (76.03, 98.79)	93.60 (81.73, 107.21)*	55.82 (47.03, 66.26)	
Solution/Fasted	85.52 (75.52, 96.85)	93.87 (81.96, 107.52)*	101.19 (85.25, 120.11)*	

[^] p<0.05 (Dunnett's test) compared to Fasted, following a statistically significant (p<0.05) overall treatment effect

* within the 80% to 125% bioequivalence limits

DISCUSSION AND COMMENTS:

d-amphetamine

These results demonstrate that for the PK population, the 90% confidence intervals (CI) of ratios of geometric means of fed vs. fasted and solution vs. fasted fell within the recommended 80.00% to 125.00% limits of average bioequivalence for AUC_{0-inf}, AUC_{0-t}, and C_{max}. These findings suggest that d-

amphetamine of NRP104 was bio-equivalent when taken with or without food or in solution.

Intact NRP104

These results demonstrate that for the PK population, 90% confidence intervals (CI) of ratios of geometric means of fed vs. fasted fell within the recommended 80.00% to 125.00% limits of average bioequivalence for AUC_{0-t} , and outside of the recommended limits for AUC_{0-inf} , and C_{max} . The 90% confidence intervals (CI) of ratios of geometric means of solution vs. fasted fell within the recommended 80.00% to 125.00% limits of average bioequivalence for AUC_{0-t} , and C_{max} , and outside of the recommended limits for AUC_{0-inf} . These findings suggest that intact NRP104 had comparable bioavailability when taken either without food or in solution, but the bioavailability was different when taken with food.

These results are not unexpected since the parent drug, intact NRP104, would be expected to be more variable than the metabolite, *d*-amphetamine.

A Pharmacokinetic Study to Assess the Rate of Absorption and the Oral Bioavailability of Two Dose Levels of NRP104 Capsules to Doses of the Reference Products, Dexedrine Spansules and Adderall XR Capsules Under Fasting Conditions-Study 104.101

**New River Pharmaceuticals
Protocol 104.101/20-636-1G**

Purpose

The primary objective of this single-dose, open-label, two-period pilot study was to compare the rate of absorption and oral bioavailability of two dose levels (1 x 25 mg and 3 x 25 mg) of the NRP104 Test Formulation to oral doses of two commercially available Reference Products, Dexedrine® Spansules (3 x 10 mg) and Adderall XR™ (1 x 30 mg + 1 x 5 mg), administered to healthy subjects after a 10-hour overnight fast.

This was not one of the main studies but was a proof of concept study.

Methods

Study Design

This was a single-dose, open-label, randomized, two-period crossover bioavailability study in which twenty healthy male and female subjects were scheduled to receive a single dose of each of two treatments within the assigned sequence in two assigned dosing periods. Each dose administration was separated by a 7-day washout period. Ten healthy subjects were assigned to each of the following sequences:

Sequence 1 (10 Subjects)	Period 1: Treatment A Period 2: Treatment C
Sequence 2 (10 Subjects)	Period 1: Treatment B Period 2: Treatment D

Dosing days were separated by a washout period of at least 7 days.

Drug administration consisted of an oral dose of the following treatments under fasting conditions:

Test Product/Level 1: Treatment A	New River Pharmaceuticals 1 x 25 mg NRP104 Capsules
Test Product/Level 2: Treatment B	New River Pharmaceuticals 3 x 25 mg NRP104 Capsules
Reference Product 1: Treatment C	GlaxoSmithKline 3 x 10 mg Dexedrine® Spansules
Reference Product 2: Treatment D	Shire USA 1 x 30 mg capsule + 1 x 5 mg Capsule Adderall XR™ Capsules

Blood samples were drawn prior to dosing (pre-dose) and at 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, and 72.0 hours post-dose.

NRP104.101

In life portion of study

Subjects dosed on: Period 1-04/26/2004; Period 2- 05/03/2004

Date of Assay

Study NRP104.101

Samples extracted for Dextroamphetamine and Levoamphetamine:

Subject(s)	Period	Dosing Date	Sample Analysis Date	# of Days Between Dosing and Analysis
All	1	4/26/2004	5/10/2004	14
All	2	5/3/2004	5/12/2004	9

Plasma Analysis Results
Assayed for d and l amphetamine.

Assay Validation

Parameter	D-Amphetamine 0.5-125 ng/ml	L-Amphetamine 0.2-50 ng/ml
Method	LC\ Mass Spectrometric \ Mass Spectrometric Detection	LC\ Mass Spectrometric \ Mass Spectrometric Detection
Freeze-thaw	4 cycles	4 cycles
Benchtop Stability at RT	6 hrs	6 hrs
Long term at -20° C	17 weeks	17 weeks
Recovery Low High	93% @ 0.5 ng/ml 85.8% @ 125ng/ml	90% @ 0.2 ng/ml 86% @ 50ng/ml

Parameter	NRP 104	Dextroamphetamine	Levoamphetamine
Method	HPLC with Mass Spectrometric Detection	HPLC with Mass Spectrometric Detection	HPLC with Mass Spectrometric Detection
Sensitivity/LOQ	1.0 ng/ml	0.5 ng/ml	0.2 ng/ml
Linearity (Standard curve samples)	1-100 ng/ml	0.5-125 ng/ml	0.2-50 ng/ml
Quality Control (QC) Samples	3, 20 and 80 ng/ml	1.5, 40 and 80 ng/ml	0.6, 16 and 32 ng/ml
Precision of Standards (%CV)	1.5 % @ 1 ng/ml 2.3 % @ 100 ng/ml	3.1 % @ 0.5 ng/ml 6.5 % @ 125 ng/ml	2.2% @ 0.2 ng/ml 7.5 % @ 50 ng/ml
Precision of QC Samples (%CV)	6 % @ 3 ng/ml 2.5 % @ 80 ng/ml	10% @ 1.5 ng/ml 6 % @ 80 ng/ml	7 % @ 0.6 ng/ml 5 % @ 32 ng/ml
Accuracy of Standards (%)	101 % @ 1 ng/ml 101 % @ 100 ng/ml	103 % @ 0.5 ng/ml 99% @ 125 ng/ml	101% @ 0.2 ng/ml 99% @ 50 ng/ml
Accuracy of QC Samples (%)	100 % @ 3 ng/ml 96 % @ 80 ng/ml	104 % @ 1.5 ng/ml 96 % @ 80 ng/ml	107 % @ 0.6 ng/ml 94 % @ 32 ng/ml

The following pharmacokinetic parameters were calculated for each subject and treatment:

C_{max}	The maximum drug concentration in plasma determined directly from individual concentration-time data
T_{max}	Time to reach maximum concentration
C_{last}	The last quantifiable drug concentration determined directly from individual concentration-time data
T_{last}	Time of the last measurable concentration
λ_z	The observed elimination rate constant; estimated by linear regression through at least three data points in the terminal phase of the log concentration-time profile for each
$T_{1/2}$	The observed terminal elimination half-life calculated as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
AUC_{last}	The area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity, calculated as: $AUC_{inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$
AUC_{Extrap} (%)	The percentage of AUC_{inf} based on extrapolation

In addition to the above pharmacokinetic parameters, oral clearance, volume of distribution, and mean residence time were calculated for NRP104 as follows:

CL/F	Total systemic clearance, not corrected for oral bioavailability (F), calculated as: $CL/F = \frac{Dose}{AUC_{inf}}$
--------	---

Dose Proportionality

Dose-proportionality of NRP104 was assessed using the results of pharmacokinetic analysis of data acquired after Treatment A (1 x 25 mg) and Treatment B (3 x 25 mg). Values of C_{max} , AUC_{last} , and AUC_{inf} for NRP104 were normalized (dose-adjusted) by dividing the parameter value by the administered dose and compared across treatment groups. The dose-normalized parameters were plotted versus the administered dose and analyzed by linear regression in Microsoft® Excel 2000. The slope and y-intercept of the linear regression line were reported along with the 95% confidence intervals.

Results

Table 1. The pharmacokinetic parameters for d-amphetamine after oral administration of NRP104

Parameter	<u>Treatment A:</u> Test Product 1 (1 x 25 mg NRP104)				<u>Treatment B:</u> Test Product 2 (3 x 25 mg NRP104)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	10	3.10	0.88	28.27	10	3.90	0.99	25.50
C _{max} (ng/mL)	10	25.0	5.57	22.27	10	74.0	12.9	17.37
AUC _{last} (hr ⁺ ng/mL)	10	396.7	84.79	21.38	10	1238	194.6	15.72
AUC _{inf} (hr ⁺ ng/mL)	10	414.9	80.32	19.36	10	1260	191.8	15.22
AUC _{Extrap} (%)	10	4.89	3.38	69.03	10	1.84	1.12	61.20
λ _z (hr ⁻¹)	10	0.0734	0.0119	16.23	10	0.0694	0.0104	14.92
T _{1/2} (hr)	10	9.66	1.45	15.02	10	10.21	1.66	16.23
T _{last} (hr)	10	45.60	7.59	16.64	10	62.40	12.39	19.86
C _{last} (ng/mL)	10	1.30	0.567	43.64	10	1.56	0.970	62.02

Table 2. Pharmacokinetic Parameters of d-Amphetamine after Oral Administration of 30 mg Dexedrine and the Racemic mixture (d+l Amphetamine) 35 mg after Oral administration of Adderall XR

Parameter	<u>Treatment C:</u> Reference Product 1 (Dexedrine)				<u>Treatment D:</u> Reference Product 2 (Adderall XR)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	10	5.80	1.40	24.11	10	5.70	2.41	42.21
C _{max} (ng/mL)	10	50.2	9.74	19.41	10	73.3	11.9	16.25
AUC _{last} (hr ⁺ ng/mL)	10	1194	235.7	19.75	10	1404	233.3	16.62
AUC _{inf} (hr ⁺ ng/mL)	10	1217	236.9	19.47	10	1429	223.3	15.62
AUC _{Extrap} (%)	10	1.94	0.87	45.03	10	1.89	1.80	95.03
λ _z (hr ⁻¹)	10	0.0636	0.0087	13.69	10	0.0716	0.0156	21.75
T _{1/2} (hr)	10	11.07	1.48	13.40	10	10.17	2.62	25.76
T _{last} (hr)	10	67.20	10.12	15.06	10	64.80	11.59	17.89
C _{last} (ng/mL)	10	1.48	0.713	48.11	10	1.61	1.30	81.04

Note: The pharmacokinetics were determined for total (d+l) amphetamine after Adderall XR

Table 3. Pharmacokinetic Parameters of NRP104 after oral administration.

Parameter	Treatment A:				Treatment B:			
	Test Product 1 (1 x 25 mg NRP104)				Test Product 2 (3 x 25 mg NRP104)			
	n	Mean	SD	CV%	n	Mean	SD	CV%
T _{max} (hr)	10	1.05	0.16	15.06	10	1.05	0.16	14.99
C _{max} (ng/mL)	10	11.6	3.80	32.87	10	53.5	34.0	63.51
AUC _{last} (hr*ng/mL)	10	11.32	3.743	33.07	10	58.11	30.24	52.05
AUC _{inf} (hr*ng/mL)	8*	13.50	3.402	25.19	10	60.02	29.73	49.54
AUC _{Extrap} (%)	8*	10.76	4.99	46.39	10	4.07	3.90	95.91
λ _z (hr ⁻¹)	8*	1.7088	0.3167	18.54	10	1.4037	0.4689	33.41
T _{1/2} (hr)	8*	0.42	0.08	18.72	10	0.57	0.24	43.23
T _{last} (hr)	10	1.95	0.16	8.11	10	3.30	0.67	20.45
C _{last} (ng/mL)	10	2.46	0.746	30.39	10	2.26	1.57	69.38
CL/F (L/hr)	8*	1945	434.2	22.32	10	1517	633.4	41.76
Vz/F (L)	8*	1193	393.8	33.01	10	1307	902.2	69.01
MRT (hr)	8*	1.23	0.19	15.61	10	1.39	0.40	28.46

*After 1 x 25 mg NRP104, there were insufficient quantifiable data to determine the elimination rate for all subjects

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-Amphetamine (Parallel Design for Comparing 75 mg NRP104 to Dexedrine)

Dependent Variable	Geometric Mean		Ratio (%) (Test/Reference)	90% Confidence Interval	
	Test	Reference		Lower	Upper
ln(C _{max})	73.0227	49.3560	147.95	128.49	170.36
ln(AUC _{last})	1223.5446	1174.2369	104.20	91.06	119.23
ln(AUC _{inf})	1246.5279	1197.4589	104.10	91.23	118.78

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-Amphetamine from NRP104 to the Racemic Mixture (*d*- + *l*-Amphetamine) from Adderall XR (Crossover Design for Comparing 75 mg NRP104 to Adderall XR)

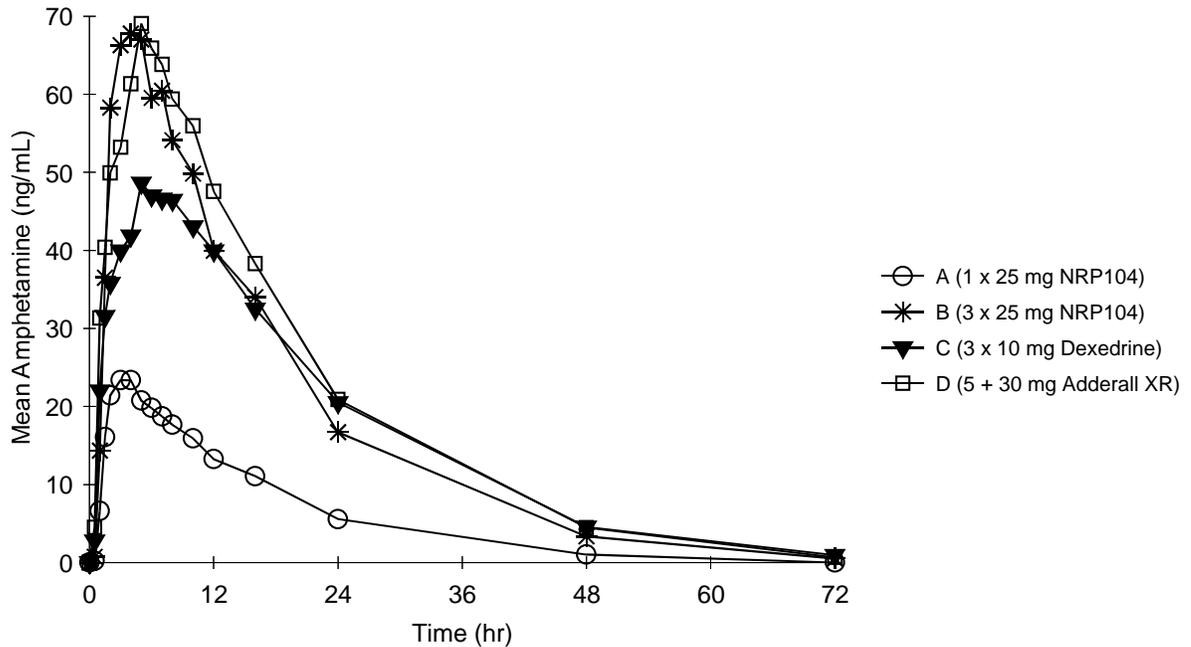
Dependent Variable	Geometric Mean		Ratio (%) (Test/Reference)	90% Confidence Interval	
	Test	Reference		Lower	Upper
ln(C _{max})	73.0227	72.3927	100.87	94.19	108.03
ln(AUC _{last})	1223.5446	1387.5133	88.18	82.98	93.71
ln(AUC _{inf})	1246.5279	1414.5184	88.12	83.85	92.62

Note: Comparisons to Adderall XR are based on total (*d*+*l*) amphetamine

Statistical Analysis of the Log-Transformed Systemic Exposure Parameters of *d*-Amphetamine (Crossover design for Comparing 25 mg NRP104 to Dexedrine after Dose-Normalization)

Dependent Variable	Geometric Mean		Ratio (%) (Test/Reference)	90% Confidence Interval	
	Test	Reference		Lower	Upper
ln(C _{max})	73.3243	49.3560	148.56	135.72	162.61
ln(AUC _{last})	1159.3989	1174.2369	98.74	88.64	109.98
ln(AUC _{inf})	1219.7728	1197.4589	101.86	92.24	112.49

Figure 1: Mean Concentration-Time Profiles for *d*-Amphetamine after NRP104 and Dexedrine and for the Racemic Mixture (*d*- + *l*-Amphetamine) after Adderall XR



A= Test Product A (*d*-amphetamine), B = Test Product B (*d*-amphetamine);
 C = Reference Product C (*d*-amphetamine), D = Reference Product D (*d*+*l*-amphetamine)

The results indicate that the T_{max} for the metabolite i.e., *d*-amphetamine is 2 hours earlier for the test products compared to Dexedrine and Adderall. A higher AUC and C_{max} were observed for *d*+*l*-amphetamine from Adderall than *d* amphetamine from Dexedrine although the doses were comparable (ie 30 mg Dexedrine-35 mg Adderall).

D-Amphetamine C_{max} and AUC were nearly proportional for the 1x25 mg and the 3x 25 mg treatments for the test product. The parent drug NRP104 showed a greater than proportional increase in C_{max} and AUC between the 1x25 mg and the 3x25 mg doses.

Comments:

1. Overall “peak exposure” based upon the geometric mean for d-amphetamine was greater for the 75 mg NRP104 tablet compared to Dexedrine as reflected by the 90% CI of 128-170. On the other hand overall exposure as determined by AUC was comparable with the 90% CI being within 80-125% of the reference product Dexedrine. It should be noted that unequal molar amounts are being compared via the same route (i.e., 75 mg NRP104 and 30 mg Dexedrine). However, 75 mg NRP104 is approximately mg of d-amphetamine compared to mg of d-amphetamine from Dexedrine.)

2. Exposure (i.e., peak-C_{max} and overall-AUC were similar) for d-amphetamine and (d+l-amphetamine) when NRP104 was compared to Adderall XR (i.e., 75 mg NRP104- mg d-amphetamine and 35 mg Adderall XR- mg d-amphetamine mg l-amphetamine).

A Single-Dose, 3 Treatment, 3-period, Crossover Pharmacokinetic Study to Assess Dose Proportionality of NRP 104 30 mg Capsules (1x30mg), 50 mg Capsules (1x50mg), and 70 mg Capsules (1x70mg) in Children Aged 6-12 years with ADHD –Protocol NRP 104.103

Study Objective:

To assess dose proportionality of d-amphetamine after oral administration of single doses of 30 mg, 50 mg, and 70 mg of NRP104 after an overnight fast to children aged 6-12 years with ADHD.

Study Design:

This trial was an open-label, single-dose, 3-treatment, 3-period, 6-sequence, randomized, crossover, Phase I dose proportionality study. The three single doses administered to subjects were NRP104 30 mg (1x30 mg), 50 mg (1x50 mg), and 70 mg (1x70 mg).

There were a total of eighteen (18) study participants, aged 6 to 12 and weighing at least 55 lbs (25 kg). They had a diagnosis of ADHD and were otherwise healthy. At the check-in of Study Period 1, subjects were randomly assigned to one of six (6) dosing sequence groups, with 3 subjects per sequence. Subjects received their assigned treatment (a single oral dose of 30 mg, 50 mg or 70 mg of NRP104) after an overnight fast of at least 8 hours during the first study period and then were crossed over to the alternate treatments for the subsequent study periods, based on their randomized dosing sequences. The washout interval was at least six (6) days between dosing days (exclusive). Subjects who discontinued the study prematurely were not replaced.

Subjects were confined to the clinic 12 hours prior to each dosing day. Confinement continued for 24 hours post dose. Fifteen (15) blood samples (3 mL per sample) were collected through the 48-hour post dose interval during each study period. These blood samples were used in determining the plasma levels of d-amphetamine and intact NRP104 at the following hours: (dose time) 0 hour, and 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 24, and 48 hours post-dose. Study medication was administered between 7:00 AM and 9:00 AM on the dosing days with 240 mL of water. Subjects were asked to swallow their capsules intact.

Meal Schedule

All subjects were required to fast for at least eight (8) hours prior to dosing. Water was allowed *ad lib.* during the study, except for one hour prior through one hour post-dose. A standard clinic evening meal (approximately 11 hours prior to dose administration) and a snack (approximately 9 hours prior to dose administration) were provided.

A validated LC/MS/MS method was used to determine plasma *d*-amphetamine and intact NRP104 concentrations for each sample. From the plasma drug levels, the following pharmacokinetic (PK) parameters (for both *d*-amphetamine and intact NRP104) were measured and calculated for bioavailability and bioequivalence evaluations at $t_{0.5}$, $t_{1.5}$, using non-compartmental methods and actual blood collection time intervals post dose:

- AUC_{0-t} : Area under the drug concentration-time curve from time zero to time t where t is the last timepoint with a drug concentration \geq LOQ (C_t).
- AUC_{0-inf} : Area under the drug concentration-time curve from time zero to infinity, $AUC_{0-inf} = AUC_{0-t} + C_t/\lambda_z$, where λ_z is the terminal elimination rate constant.
- $t_{1/2}$: Elimination half-life calculated as $0.693/\lambda_z$.
- C_{max} : Maximum observed drug concentration.
- T_{max} : Time at which C_{max} occurs.

To evaluate the dose proportionality, C_{max} , AUC_{0-t} , and AUC_{0-inf} of the 30 mg and 70 mg doses were normalized to the 50 mg dose and analyzed on the natural logarithmic scale using the same ANOVA model described above. Ninety percent (90%) confidence intervals (CI) for the geometric mean ratios (30 mg-50 mg, 70 mg-50 mg) were calculated. According to the two one-sided t-test procedures at 0.05 level of bioequivalence, dose proportionality was concluded if the 90% CIs fell within 80.00% \rightarrow 125.00% (or 0.80 \rightarrow 1.25) for both the 30 mg vs. 50 mg pair and the 70 mg vs. 50 mg pair.

In addition, linearity was examined using the power model, i.e. $P = a \times \text{Dose}^b$, where P represents C_{max} or AUC and, a and b were constants. A value of $b \approx 1$ indicates linearity.

Subject Demographics

Table 3 Demographic and Baseline Characteristics of Randomized Population		
Characteristic	Category/Parameter	Total (N=18)
Race (%)	Caucasian	8 (44%)
	African American	8 (44%)
	Native American	1 (6%)
	Other (Asian American)	1 (6%)
Gender (%)	Male	10 (56%)
	Female	8 (44%)
Height (inches)	Mean	54.8
	SD	4.0
	Median	54.8
	Min-Max	49.5 – 62.0
Weight (pounds)	Mean	80.0
	SD	16.8
	Median	78.8
	Min-Max	56.0 – 104.5
Age (years)	Mean	9.6
	SD	1.9
	Median	10.0
	Min-Max	6.0 – 12.0

Source: Section 15 Table 1.2.1

Results

Plasma Analysis Results: NRP104.103

Study NRP104.103

Subject(s)	Period	Dosing Date	Sample Analysis Date	# of Days Between Dosing and Analysis
1-18	1	9/11/2004	9/23/2004	12
1-17	2	9/19/2004	9/28/2004	9
1-9	3	9/25/2004	9/30/2004	5
10-17	3	9/25/2004	10/4/2004	9

In life portion of study

Subjects dosed on: Period 1-09/11/2004; Period 2- 09/19/2004; Period 3-09/25/2004

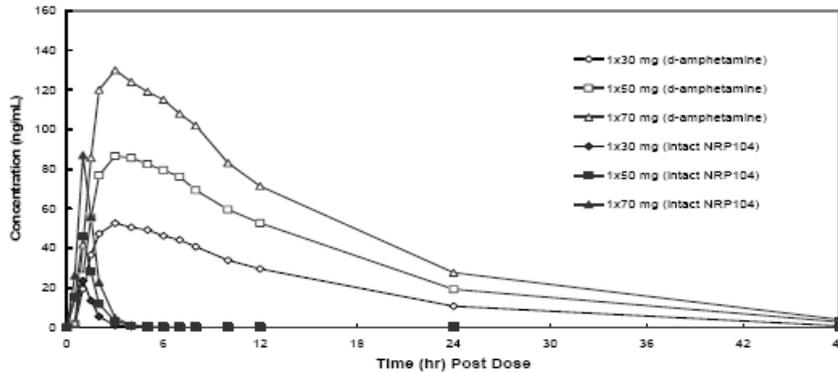
Total storage time: 12 days

Parameter	NRP-104	d-amphetamine
Method	HPLC with Mass Spectrometric Detection	HPLC with Mass Spectrometric Detection
Sensitivity/LOQ	1 ng/ml	2 ng/ml
Linearity (Standard curve samples)	1-100 ng/ml	2-200 ng/ml
Quality Control (QC) Samples	3, 20 and 80 ng/ml	6, 40, and 160 ng/ml
Precision of Standards (%CV)	3.9% @ 1 ng/ml 2.8 % @ 100 ng/ml	1.8% @ 2 ng/ml 5 % @ 200 ng/ml
Precision of QC Samples (%CV)	13 % @ 3 ng/ml 5 % @ 80 ng/ml	8 % @ 6 ng/ml 5 % @ 160 ng/ml
Accuracy of Standards (%)	101 % @ 1 ng/ml 97 % @ 100 ng/ml	99% @ 2 ng/ml 95 % @ 200 ng/ml
Accuracy of QC Samples (%)	92 % @ 3 ng/ml 99 % @ 80 ng/ml	99 % @ 6 ng/ml 105 % @ 160 ng/ml

Summary of Pharmacokinetic Results:

PHARMACOKINETICS:

**Average Plasma Drug Concentration-Time Plot:
d-amphetamine and Intact NRP104**



d-Amphetamine

PK Parameters: Mean

	AUC _(0-inf) (ng.hr/mL)	AUC _(0-t) (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
NRP104 1x30 mg	844.6	745.3	53.2	3.41
NRP104 1x50 mg	1510	1448	93.3	3.58
NRP104 1x70 mg	2157	2088	134	3.46

Bioequivalence (dose-normalized to 50 mg): % Ratio (90% CI)

30 mg to 50 mg	93.28 (87.36, 99.60)*	85.66 (79.12, 92.74)	95.25 (90.56, 100.17)*
70 mg to 50 mg	101.62 (95.34, 108.31)*	102.42 (94.80, 110.65)*	102.36 (97.46, 107.51)*

Power Model: $P = a \times \text{Dose}^b$

b constant	1.1027	1.2191	1.0887
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Intact NRP104

PK Parameters: Mean (SD)

	AUC _(0-inf) (ng.hr/mL)	AUC _(0-t) (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
NRP104 1x30 mg	27.88	25.54	21.9	0.97
NRP104 1x50 mg	57.90	56.20	46.0	0.98
NRP104 1x70 mg	108.9	107.4	89.5	1.07

Bioequivalence (dose-normalized to 50 mg): % Ratio (90% CI)

30 mg to 50 mg	78.55 (69.16, 89.23)	74.83 (65.60, 85.36)	84.31 (69.57, 102.17)
70 mg to 50 mg	130.27 (115.08, 147.45)	132.96 (116.97, 151.12)	141.71 (117.55, 170.84)

Power Model: $P = a \times \text{Dose}^b$

b constant	1.5452	1.6308	1.5826
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* within the 80% to 125% bioequivalence limits

Table 11 below summarizes the PK parameters of AUC and C_{max} of *d*-amphetamine for boys vs. girls, with and without dose-normalized to mg/Kg, in the PK population.

Table 11 PK Parameters for <i>d</i>-amphetamine with and without Dose-Normalized to mg/Kg for Sub-Groups (PK Population)			
Sub-Group\PK Parameters	AUC _{0-inf} (ng hr/mL)	AUC _{0-t} (ng hr/mL)	C _{max} (ng/mL)
Un-Normalized: Boys (10)	1448.92	1374.01	88.17
Girls (7)	1632.14	1555.10	104.11
Normalized (mg/Kg): Boys (10)	1108.78	1038.16	67.00
Girls (7)	1034.46	975.99	65.75
Un-Normalized: 6-9 yrs (6)	1694.02	1619.44	112.96
10-12 yrs (11)	1431.82	1355.38	84.80
Normalized (mg/Kg): 6-9 yrs (6)	1021.34	967.60	67.19
10-12 yrs (11)	1109.18	1037.09	66.11

Source: Section 15 Table 2.1.1

Comment:

1. The results of the power model analysis ($P = a \times \text{Dose}^b$) indicated that the pharmacokinetics of the parent drug are non-linear whereas the pharmacokinetics of the metabolite *d*-amphetamine are linear in the dose range of 30mg to 70 mg.
2. Apparently higher exposure in girls when normalized to by dose (mg/kg), the difference disappears.
3. For intact NRP, systemic exposure was about 30-40% higher in girls than in boys; and in 6-9 yrs olds than in 10-12 yrs olds. When the exposure parameters (AUC and C_{max}) were normalized by dose (mg/Kg), these differences reduced to 10-20% (Section 15 Table 2.1.2).

A Multiple-Dose Single-Arm Pharmacokinetics Study of NRP104 70 mg Capsules (1x70mg) Following 7-day administration in healthy Adult Volunteers Under Fasting Conditions Protocol 104.104

Objective:

To assess steady-state pharmacokinetics of *d*-amphetamine of NRP104 70 mg (1x70 mg) in healthy adult volunteers following the drug administration of seven consecutive days and under fasting condition.

Study Design

This was an open-label, multiple-dose Phase I study to assess the pharmacokinetics, tolerability and safety of NRP104 70mg capsules. NRP104 70 mg capsules (1x70 mg) were administered to each subject once daily in the morning for seven consecutive days. Subjects received dose on an outpatient basis Days 1 through Day 6. Subjects visited the research center in the morning at Day 1 through Day 6 to have the dose administered. Subjects returned to the research center the evening of Day 6 to ensure an overnight fast prior to dosing on Day 7. Subjects continued to fast through at least 4 hours following drug administration on Day 7.

The study consisted of a pre-study screening followed by seven consecutive days of dosing with NRP104 70 mg (1x70 mg) capsules and subsequent outpatient visits for pharmacokinetic and clinical assessment. Following the screening visit, eligible subjects were contacted by site personnel via telephone to inform the subject that he or she met all of the entering criteria. Eligible subjects were scheduled to return to the clinic for each outpatient dosing (Days 1-6). Subjects returned to the research center on the evening of Day 6 to having an overnight confinement. Subjects received the last dose of NRP104 70 mg on the morning of Day 7. Clinical and pharmacokinetic assessments were performed as indicated below. The study enrolled twelve (12) healthy adults aged 20 to 46 years. The following events occurred during study participation:

Meal Schedule

On Day 6 a standard clinic snack (approximately 11 hours prior to dose administration) was served the evening of check-in. All subjects were required to fast for at least ten (10) hours prior to Day 7 dosing. Water was allowed *ad lib.* during the study, except for one (1) hour prior through two (2) hours post Day 7 dose.

All subjects continued to fast through at least four (4) hours following Day 7 drug administration, at which time a standard clinic menu and meal schedule was followed. The hours listed below were approximate in relation to time of dosing:

Lunch:	4-5 hours post dose
Dinner:	9-10 hours post dose
Evening snack:	13-14 hours post dose

Blood Collection for Quantification of *d*-amphetamine and Intact NRP104

On the morning of Day 1, Day 5, and Day 6, one venous blood sample (7 mL) was drawn into an EDTA vacutainer tube prior to the administration of the study drug.

On Day 7 and after, venous blood samples (1x7 mL) were drawn into an EDTA vacutainer tube at the following times: (Dose time) 0 hour and 0.5, 1.0, 1.5, 2, 3, 4, 5, 6, 7, 8, 10, 12, 16, 24, 48, and 72 hours post-dose.

There were 20 blood samples collected during the study. Approximately 140 mL of blood were collected from each subject for PK analysis.

Subject Demographics

Table 3 Demographic and Baseline Characteristics of Randomized Population		
Characteristic	Category/Parameter	Total (N=12)
Ethnicity/Race (%)	Caucasian	6 (50%)
	Hispanic	6 (50%)
Gender (%)	Male	4 (25%)
	Female	8 (75%)
Height (cm)	Mean	167.1
	SD	9.8
	Median	162.8
	Min-Max	158.0 – 183.5
Weight (kg)	Mean	68.5
	SD	10.7
	Median	66.8
	Min-Max	55.1 – 84.4
Age (years)	Mean	37.0
	SD	8.9
	Median	40.0
	Min-Max	20.0 – 48.0

Source: Section 15 Table 1.2.1

Samples		
Precision of Standards (%CV)	1.4 %@ 2 ng/ml 4.2 %@ 200 ng/ml	NR%@ 1 ng/ml NR%@ 100 ng/ml
Precision of QC Samples (%CV)	5%@ 6 ng/ml 6 %@ 160 ng/ml	8 %@ 3 ng/ml 15%@ 80 ng/ml
Accuracy of Standards (%)	100 %@ 2 ng/ml 103 %@ 200 ng/ml	99%@ 1 ng/ml 97%@ 100 ng/ml
Accuracy of QC Samples (%)	98 %@ 6 ng/ml 98 %@ 160 ng/ml	94 %@ 3 ng/ml 101 %@ 80 ng/ml

Results

Pre-Dose Concentration

Table 4 below presents plasma *d*-amphetamine concentrations obtained at pre dose, including Day 1 and Day 8 (i.e., 24-hour post Day-7 dose). The regression analysis on the pre-dose concentration data obtained from Day 5 to Day 7 revealed a slope estimate of 0.6543 (95% confidence interval: -5.1616 to 6.4701) and an associated *p* value of 0.82 (Appendix Section 16.1.9.2, Page 22). This finding suggests that the steady state concentrations of *d*-amphetamine were achieved by Day 5 and the slope of the trough concentrations represented a near flat line from Day 5 to Day 7. The Day-8 concentration (i.e., through concentration 24-hour post Day-7 dose) is also reported in Table 4, which further confirmed that steady state concentrations of *d*-amphetamine were achieved by Day 5.

Dosing Day	Day 1	Day 5	Day 6	Day 7	Day 8 (24-hr post Day-7 dose)
N	11	11	11	11	11
Mean	0.0	20.6	18.7	21.9	18.2
S.D.	0.0	11.8	10.7	17.2	10.7
CV%	-	57.24	57.01	78.48	59.01

Source: Appendix Section 16.1.9.2, Pharmacokinetic and Bio-analytical Analysis Report, Page 13.

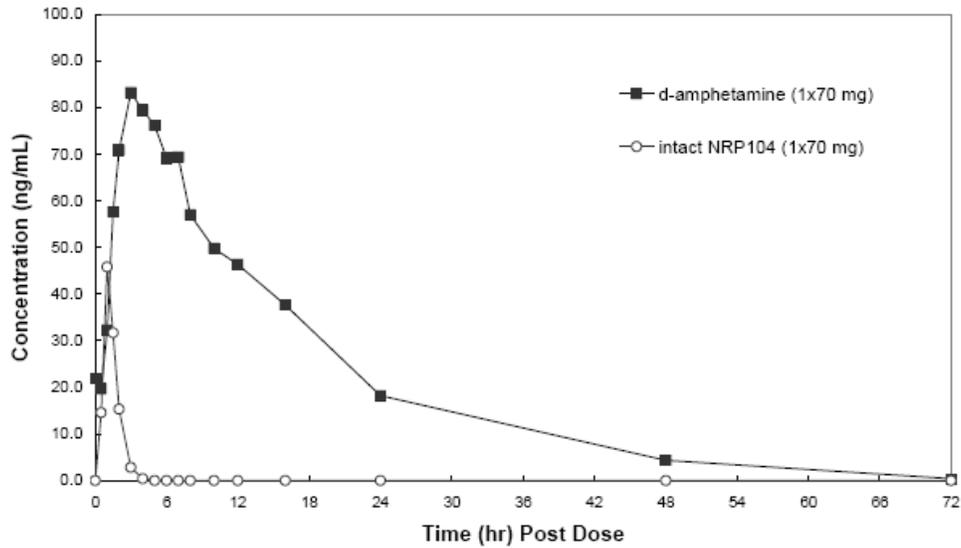
Table 6 below presents plasma intact NRP104 concentrations obtained at pre dose, including Day 1 and Day 8 (i.e., 24-hour post Day-7 dose). No quantifiable concentrations were noted at Day 5 to Day 7 for intact NRP104, suggesting that there was no drug accumulation for intact NRP104 following the administration of multiple daily doses of 70 mg per day.

Table 6 Mean and S.D. of Pre-Dose Plasma Intact NRP104 Concentration (ng/mL)					
Dosing Day	Day 1	Day 5	Day 6	Day 7	Day 8 (24-hr post Day-7 dose)
N	11	11	11	11	11
Mean	0.0	0.0	0.0	0.0	0.0
S.D.	0.0	0.0	0.0	0.0	0.0
CV%	-	-	-	-	-

Source: Appendix Section 16.1.9.2, Pharmacokinetic and Bio-analytical Analysis Report, Page 13.

**SUMMARY RESULTS
PHARMACOKINETICS:**

**Steady State Plasma Drug Concentration-Time Plot (fasted):
d-amphetamine and intact NRP104**



d-Amphetamine

	PK Parameters			
	AUC _(0-inf) (ng.hr/mL)	AUC ₍₀₋₂₄₎ (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
N	11	11	11	11
Mean	1453	1113	90.1	3.68
SD	645.7	396.8	29.6	1.42

Intact NRP104

	PK Parameters			
	AUC _(0-inf) (ng.hr/mL)	AUC ₍₀₋₂₄₎ (ng.hr/mL)	C _{max} (ng/mL)	T _{max} (hr)
N	11	11	11	11
Mean	61.06	60.66	47.9	1.14
SD	20.63	21.00	18.6	0.32

On Day 7, the arithmetic mean \pm standard deviation was 60.66 ± 21.00 for AUC₀₋₂₄ (ng•hr/mL), 61.06 ± 20.63 for AUC_{0-inf} (ng•hr/mL), 59.44 ± 21.47 for AUC_{0-t} (ng•hr/mL), 47.9 ± 18.6 for C_{max} (ng/ml), and $1.14 \pm$ for T_{max}(hr).

Sub-group Analysis

PK parameters AUC and C_{max} of *d*-amphetamine and intact NRP104 were summarized descriptively for sub-groups of men vs. women with and without dose normalized to mg/Kg. The mg/Kg normalization was calculated by multiplying a PK parameter by a factor of (Weight/Dose) for each subject, where the Weight was the subject's body weight (kg) and Dose was the dosage (70 mg) given. The results are reported in Section 15 Table 2.1.1 for *d*-amphetamine and Table 2.1.2 for intact NRP104.

Table 8 below summarizes the PK parameters of AUC and C_{max} of *d*-amphetamine for men vs. women, with and without dose-normalized to mg/Kg, in the PK population.

Table 8 PK Parameters for <i>d</i> -amphetamine with and without Dose-Normalized to mg/Kg for Sub-Groups (PK Population)			
Sub-Group\PK Parameters	AUC _{0-inf} (ng hr/mL)	AUC _{0-t} (ng hr/mL)	C _{max} (ng/mL)
Un-Normalized: Men (4)	1419.79	1339.97	81.27
Women (7)	1471.22	1389.32	95.10
Normalized (mg/Kg): Men (4)	1676.86	1582.88	95.92
Women (7)	1296.59	1224.19	83.87

Source: Section 15 Table 2.1.1

Systemic exposure to *d*-amphetamine was about the same in both men and women for AUC parameters; and, was about 17% higher in women (n=7) than in men (n=4) for C_{max} , due to the higher dose administered to women on a mg/Kg body weight basis. When the exposure parameters (AUC and C_{max}) were normalized by body weight to mg/Kg, the difference in C_{max} changed with men being higher of 12% than women.

For intact NRP, systemic exposure was comparable in women than in men. When the exposure parameters (AUC and C_{max}) were normalized by body weight to mg/Kg, the systemic exposure seems to have been higher of about 25% to 35% in man than in women

11.4.4 Conclusions of PK Data

Following daily dose administration of NRP104 70 mg, steady state concentrations of *d*-amphetamine were achieved by Day 5. Dosed with 70 mg per day, intact NRP104 was seen to have been completely eliminated approximately 6 hours post dose.

At steady state, the average of PK parameters obtained for *d*-amphetamine was 1453 for AUC_{0-inf} (ng•hr/mL), 1113 for AUC₀₋₂₄ (ng•hr/mL), 90.1 for C_{max} (ng/mL), and 3.68 for T_{max} (hr). The average of PK parameters obtained for intact NRP104 was 61.06 for AUC_{0-inf} (ng•hr/mL), 59.44 for AUC_{0-t} (ng•hr/mL), 47.9 for C_{max} (ng/mL), and 1.14 for T_{max} (hr).

Comment:

1.The normalized *d*-amphetamine AUC and C_{max} values were 22% and 12% lower respectively in women compared to men.

Mass Balance and Elimination Profiles of NRP-104 ¹⁴C and Radioactive Metabolites

New River Pharmaceuticals Inc. Protocol NRP-104.106

Primary Objective:

- To assess the distribution, metabolism, and elimination of NRP-104 radiolabeled with ¹⁴C in normal healthy subjects following a single oral solution dose administration.

Secondary Objective:

- To assess the safety and tolerability of NRP-104 radiolabeled with ¹⁴C in normal healthy subjects following a single oral solution dose administration.

Trial Design

This was a single center, open-label study to assess the distribution, metabolism, elimination and safety profile of NRP-104 radiolabeled ¹⁴C in normal healthy subjects. Subjects were accommodated in a Phase I unit for the duration of their study participation.

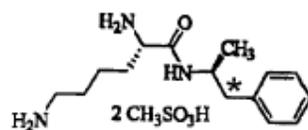
Each of six subjects received a single oral solution dose of 70 mg ¹⁴C radiolabel NRP-104 in 60 mL to contain 108 µCi of ¹⁴C radioactivity. The dose was administered over a maximum 1 minute dosing period.

Study Events Outline

- Pre-study screening; blood, urine and feces samples.
- Received a single oral solution, 1 x 70 mg dose on the morning of Study Day 1 following a minimum 10-hour overnight fast.
- Blood draws for pharmacokinetic analysis were collected at pre-dose, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 24.0, 36.0, 48.0, 72.0, 96.0, and 120.0 hours post dose
- Blood draws for radioanalysis were collected at pre-dose, 0.5, 1.0, 1.5, 2.0, 3.0, 4.0, 5.0, 6.0, 7.0, 8.0, 10.0, 12.0, 16.0, 24.0, 48.0, 72.0, 96.0 and 120.0 hours post dose
- Urine for radioanalysis and metabolite profiling was collected at time intervals as follows: pre-dose and 0-4, 4-8, 8-12, 12-16, 16-20, 20-24, 24-36, 36-48, 48-60, 60-72, 72-84, 84-96, 96-108 and 108-120 hours post-dose.
- Fecal samples were collected at the following intervals: pre-dose and 0-12, 12-24, 24-48, 48-72, 72-96 and 96-120 hours post-dose, as available.

Dose Preparation

The dose formulation of the NRP-104-¹⁴C test article was prepared (May 5, 2005) on the day before the dosing by dissolving 550 mg of the non-radioactive crystals of NRP-104 in 470 mL sterile water. To this solution was added 10.0 mL ethanolic solution of 1.0 mCi of NRP-104-¹⁴C to yield a target concentration of 1.16 mg/mL at a specific radioactivity of 1.55 µCi/mg. Prior to dosing, the radioactivity concentration and purity were checked by counting triplicate aliquots by liquid scintillation counting (LSC), and by . The HPLC radioactivity profile showed a single peak at the retention time of NRP-104. The mean radioactivity concentration was used in the calculation of the amount of radioactivity administered to each volunteer. At the time of dosing, each volunteer consumed 60 mL of the dose formulation (=70.0 mg of NRP-104 = 153.6 µMol; containing 108 µCi = 237.5 x 10⁶ dpm).



NRP-104 C₁₅H₂₅N₃O

Mol. Wt.: 455.59

(Mol. Wt.: 263.38 as free base)

Figure 1: Structure of NRP-104-¹⁴C

Radioanalytical Methods

Liquid Scintillation Counting

All samples directly counted by liquid scintillation counting (LSC) were analyzed using [redacted] scintillation [redacted]. All samples were counted in a [redacted] liquid scintillation analyzer [redacted] for 5 minutes. The LSC data (counts per minute; cpm) were automatically corrected for counting efficiency using an external standardization technique and an [redacted] obtain disintegrations per minute (dpm). The LSC data were corrected for background by subtracting the dpm value measured from the analysis of a blank sample.

Radioanalysis of Urine

Total Radioactivity in Urine

Each sample was mixed thoroughly and duplicate aliquots (0.050 mL) were transferred to scintillation vials, mixed with 10 mL [redacted] LSC fluid and counted for 5 minutes in a [redacted] counter. The dpm/mL was calculated and multiplied by the total urine volume for that interval and divided by the total dpm administered in the dose to determine the percent of the dose excreted.

NRP104.106

Study NRP104.106

Subject(s)	Dosing Date	Sample Analysis Date	# of Days Between Dosing and Analysis
101-106	5/6/2005	6/1/2005	26

Total storage time is 26 days.

Plasma Analysis Results

Parameter	Amphetamine	NRP-104
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	N=2 runs	N=2 runs
Method	HPLC with Mass Spectrometric Detection	HPLC with Mass Spectrometric Detection
Sensitivity/LOQ	2 ng/ml	1 ng/ml
Linearity (Standard curve samples)	2-200 ng/ml	1-100 ng/ml
Quality Control (QC) Samples	6,40 , and 160 ng/ml	3, 20 and 80 ng/ml
Precision of Standards (%CV)	NA	NA
Precision of QC Samples (%CV)	2 %@ 6 ng/ml 1.4 %@ ng/ml	1.4 %@ 3 ng/ml 4.9 %@ 80 ng/ml
Accuracy of Standards (%)	102%@ ng/ml 97%@ ng/ml	100%@ ng/ml 106 %@ ng/ml
Accuracy of QC Samples (%)	106 %@ 6 ng/ml 105 %@ 160 ng/ml	107 %@ 3 ng/ml 98 %@ 80 ng/ml

Pharmacokinetic Analysis

Data from 6 subjects who completed the study were included in the pharmacokinetic analysis. The concentration-time data were transferred from directly to WinNonlin Enterprise Edition (Version 4.0, Pharsight Corporation) using the Custom Query Builder option for analysis. Data were analyzed by noncompartmental methods in WinNonlin. Concentration-time data that were BLQ (< 1.00 ng/mL for NRP104 and < 2.00 ng/mL for amphetamine) were treated as zero (0.00 ng/mL) in the data summarization and descriptive statistics. In the pharmacokinetic analysis, BLQ concentrations were treated as zero from time-zero up to the time at which the first quantifiable concentration was observed; embedded and/or terminal BLQ concentrations were treated as “missing”. Full precision concentration data and actual elapsed times were used for all pharmacokinetic analyses.

Pharmacokinetic Methods

The following pharmacokinetic parameters were calculated:

C_{max}	The maximum drug concentration in plasma determined directly from individual concentration-time data
T_{max}	Time to reach maximum concentration
C_{last}	The last quantifiable drug concentration determined directly from individual concentration-time data
T_{last}	Time of the last measurable concentration
λ_z	The observed elimination rate constant; estimated by linear regression through at least three data points in the terminal phase of the log concentration-time profile
$T_{1/2}$	The observed terminal elimination half-life calculated as: $T_{1/2} = \frac{\ln(2)}{\lambda_z}$
AUC_{last}	The area under the plasma concentration-time curve from time-zero to the time of the last quantifiable concentration; calculated using the linear trapezoidal rule
AUC_{inf}	Area under the concentration-time curve from time-zero extrapolated to infinity, calculated as: $AUC_{inf} = AUC_{last} + \frac{C_{last}}{\lambda_z}$
$AUC_{Extrap} (\%)$	The percentage of AUC_{inf} based on extrapolation

RESULTS

Per Cent of Dose Recovered in Urine and Feces

Subject	% Dose excreted		Total % Recovered
	Urine (0-120 hr)	Feces (0-108 hr)	
101			
102			
103			
104			
105			
106			
Mean (n=6)	96.4	0.28	96.7

Table 20: Comparison of Plasma Total Mean Radioactivity (nmol-eq/mL) with the Mean Concentrations of NRP104 Plus Amphetamine (nmol/mL) Determined by LC-MS-MS

Time (hr)	Mean Total Radioactivity* (nmol-eq/mL)	Mean AMP ^b (ng/mL by LC-MS-MS)	Mean AMP ^b (nmol/mL by LC-MS-MS)	Mean NRP104 ^b (ng/mL by LC-MS-MS)	Mean NRP104 ^b (nmol/mL by LC-MS-MS)	Mean AMP + NRP104 (nmol/mL by LC-MS-MS)	Difference nmol/mL ^c
0	0.00	0.00	0.00	0.00	0.00	0.00	0.00
0.5	0.228	3.97	0.0293	38.5	0.148	0.175	0.0530
1	0.500	34.0	0.252	53.4	0.208	0.455	0.0458
1.5	0.633	55.0	0.407	19.1	0.0728	0.480	0.1533
2	0.694	65.2	0.482	8.60	0.0326	0.515	0.1789
3	0.719	72.6	0.537	3.32	0.0126	0.550	0.1698
4	0.704	67.7	0.501	1.99	0.00755	0.508	0.1951
5	0.752	69.6	0.515	2.68	0.0102	0.525	0.2272
6	0.674	65.6	0.485	0.554	0.00210	0.487	0.1869
7	0.632	61.4	0.454	0.188	0.000712	0.455	0.1768
8	0.627	57.2	0.423	0.00	0.00	0.423	0.2042
10	0.534	47.3	0.350	0.00	0.00	0.350	0.1840
12	0.501	43.1	0.319	0.00	0.00	0.319	0.1827
16	0.439	33.8	0.250	0.00	0.00	0.250	0.1885
24	0.300	18.4	0.138	0.00	0.00	0.138	0.1634
48	0.0897	3.75	0.0278	0.00	0.00	0.028	0.0819
72	0.0458	0.00	0.00	0.00	0.00	0.00	0.0458
96	0.0210	0.00	0.00	0.00	0.00	0.00	0.0210
120	0.0215	0.00	0.00	0.00	0.00	0.00	0.0215

**Table 27: Radioactivity in Packed Red Cells^a
NRP-104.106 ¹⁴C Mass Balance Study**

Subject	Time (hr)	DPM1	DPM2	Mean DPM
101	0			0.00
	1			279
	6			373
102	1			434
	6			531
103	1			269
	6			509
104	1			51.2
	6			466
105	1			333
	6			377
106	1			518
	6	470		

Table 28: Summary of NRP-104 and Metabolites in 0-48 Hour Urine as a Percentage of the Administered Dose

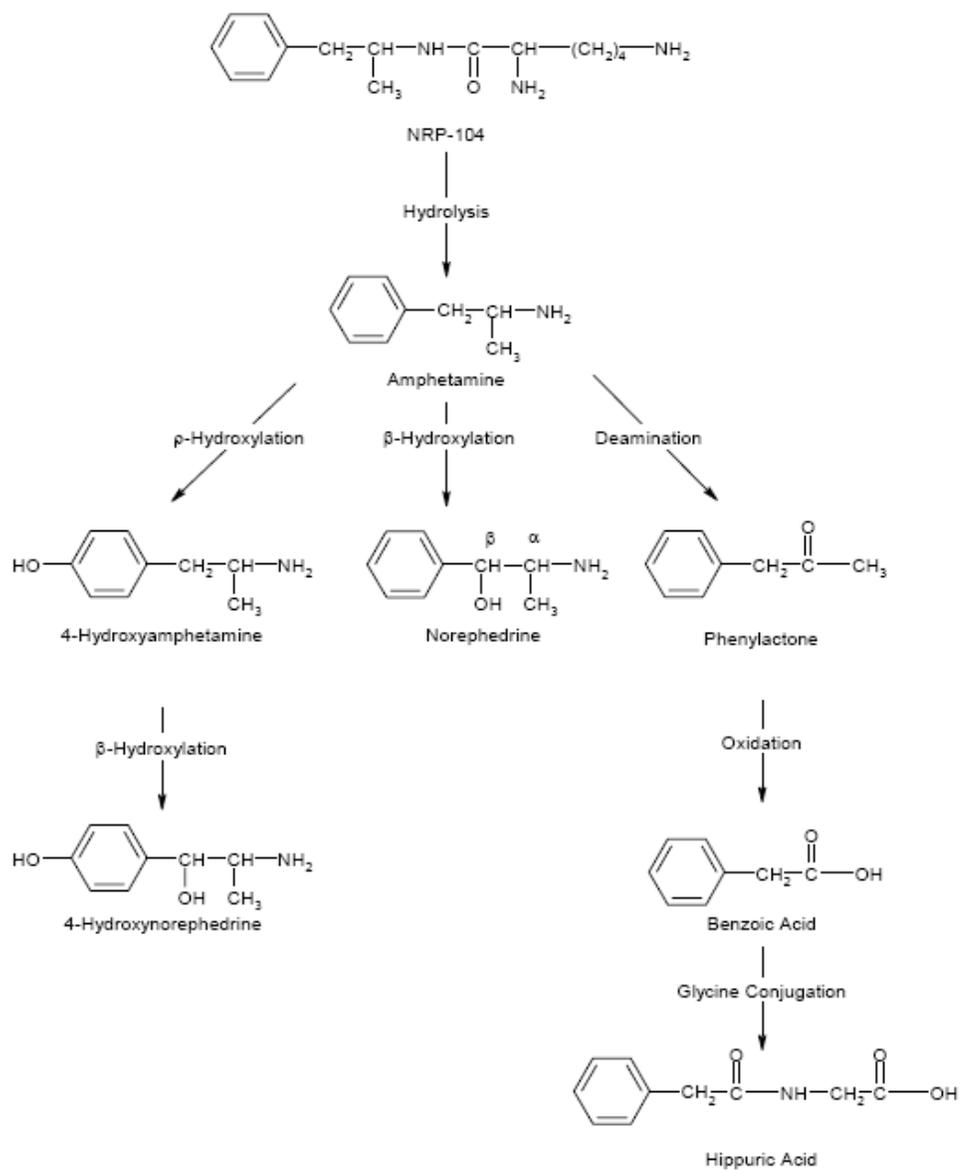
Subject	Percentage of Radioactive Dose Administered					
	NRP104	AMP	HPA	BA	Other	Total
101						
102						
103						
104						
105						
106						
Average (%) of Dose	2.2	41.5	24.8	2.2	8.9	79.4

Table 29: Tabular Summary of NRP-104 and its Metabolites Detected in Plasma, Urine, and Feces from Humans Following a Single Oral Dose of NRP-104-¹⁴C

Matrix	Parent NRP-104	Metabolites				% of Radioactive Dose Found in Matrix
	NRP-104	AMP	HPA	BA	Other	
Plasma	D	M	N	N	N	N
Urine	R	M	M	R	R	96.4
Feces	N	N	N	N	N	< 0.30

D = Detected by LC-MS-MS
M = Major metabolite in each sample
R = Detected by radioactivity
N = Did not determine identity of radioactivity

Figure 5 Proposed Metabolic Pathways Schematic



Dissolution data

TEST METHOD DESCRIPTION

Samples (n=12 each) were tested as described in [REDACTED] Method [REDACTED] except that the dissolution media were substituted. USP Apparatus 2 at 50 rpm was used with 900 mL of dissolution medium at 37.0 ± 0.5 °C. Media included 0.1 N HCl (current method), water, 0.05 M acetate buffer at pH 4.5, 0.05 M phosphate buffer at pH 6.5, and 0.05 M phosphate buffer at pH 7.5. The various buffers were prepared as described in USP 27 (p. 2724). Samples were removed at 10-, 15-, 20-, 30-, and 45-minute time points. The amount of NRP-104 released was determined by HPLC analysis versus standards prepared in the same media. The analytical procedure is described in detail in [REDACTED] Method [REDACTED]

Only data from the 0.1N HCL method will be presented since for the other media dissolution was [REDACTED]% complete by 10 min.

TABLE I

**DISSOLUTION PROFILE RESULTS OBTAINED FOR NRP-104 30-MG
CAPSULES IN 0.1 N HCL**

Sample Identification: NRP-104 30-mg Capsules, Lot No. 3040333R
Dissolution Medium: 0.1 N HCl
Method No: [REDACTED]

Number	Percent of Label Released				
	<u>10min</u>	<u>15min</u>	<u>20min</u>	<u>30min</u>	<u>45min</u>
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	95.3	100.6	101.3	101.3	101.3
RSD (%)	10.5	2.0	1.4	1.5	1.5

TABLE VI

DISSOLUTION PROFILE RESULTS OBTAINED FOR NRP-104 50-MG CAPSULES IN 0.1 N HCL

Sample Identification: NRP-104 50-mg Capsules, Lot No. 3040412R
Dissolution Medium: 0.1 N HCl
Method No: [REDACTED]

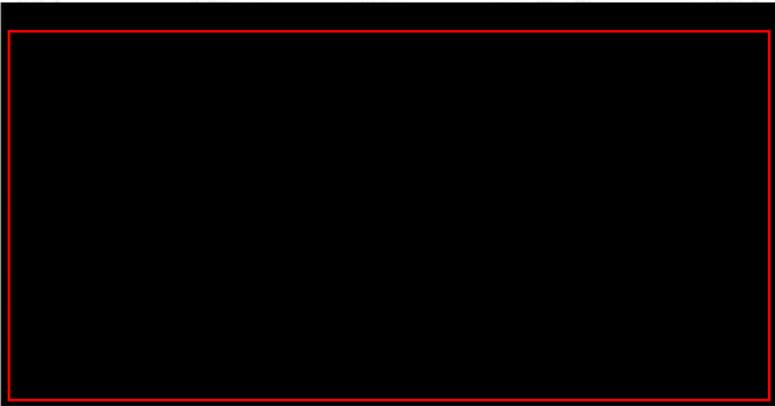
<u>Number</u>	<u>Percent of Label Released</u>				
	<u>10min</u>	<u>15min</u>	<u>20min</u>	<u>30min</u>	<u>45min</u>
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	86.1	96.6	99.9	101.5	101.9
RSD (%)	11.4	7.2	5.2	3.8	3.4

TABLE XI

**DISSOLUTION PROFILE RESULTS OBTAINED FOR NRP-104 70-MG
CAPSULES IN 0.1 N HCL**

Sample Identification: NRP-104 70-mg Capsules, Lot No. 3040464R
Dissolution Medium: 0.1 N HCl
Method No:

Number	Percent of Label Released				
	10min	15min	20min	30min	45min
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					
Average	93.2	97.7	98.4	99.0	98.8
RSD (%)	9.3	3.8	2.7	2.2	2.2

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/s/

Andre Jackson
8/4/2006 09:08:29 AM
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Raman Baweja
8/4/2006 11:15:43 AM
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