Lisdexamfetamine Dimesylate (NRP104 / LDX) Clinical Abuse Liability Studies

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Forward-Looking Statements

This presentation may contain forward-looking statements that reflect management's current views as to New River Pharmaceuticals Inc.'s clinical trials, regulatory approval process, product development, research programs and other future events and operations. These forward-looking statements involve uncertainties and risks that are detailed in New River Pharmaceutical Inc.'s Annual Report on Form 10-K filed with the SEC on March 15, 2006, as well as other public filings with the SEC. Actual results could differ materially from these forward-looking statements.

Study A01

A Single-Blind, Placebo- and Active-Controlled, Single-Dose Escalation Study of NRP104 (up to 150 mg) to Evaluate Safety, Tolerability, and Abuse Liability in Healthy Adult Volunteers with Histories of Stimulant Abuse

Study A01

Treatment

- 3 Cohorts of 4 subjects each
  - each of 12 subjects received 4 single doses of NRP104 in a dose-escalation fashion, 1 single dose of *d*-amphetamine, and 1 dose of placebo
- Minimum 2-day interval between dosing
- PK and PD measures before dosing and at 0.5, 1, 1.5, 2, 3, 4, 5, 6, 9, 12, 16 and 24 hours after dosing

Cohort	Placebo	*d*-Amphetamine, mg	NRP104, mg					
1	Yes	40	30	50	70	100		
2	Yes	40		50	70	100	130	
3	Yes	40			70	100	130	150

Study A01

Subject Eligibility

- All subjects had history of stimulant abuse
- No other clinically significant Axis I psychiatric disorders other than substance abuse
- Could not be currently physically dependent on
  - benzodiazepines (urine drug screen)
  - opiates (naloxone challenge, 0.4 mg and 1 mg)
  - ETOH (Breathalyzer test)
- No concomitant medications allowed (other than female hormonal contraceptives or HRT)
- Minimum Grade 6 reading level as determined by the Rapid Estimation of Adult Literacy in Medicine (REALM)

Study A01

Demographics and Baseline Characteristics

Characteristic	N = 12
Age, years	
Mean ± SD	43 ± 5.9
Median (range)	44 (29 – 52)
Sex, n (%)	
Male	12 (100)
Race, n (%)	
White	1 (8.3)
Black	10 (83.3)
Asian	1 (8.3)
Height, cm	
Mean ± SD	172.8 ± 6.7
Median (range)	174 (160 – 183)
Weight, kg	
Mean ± SD	74.6 ± 10.8
Median (range)	72 (58 – 94)
REALM test score	
Mean ± SD	61.8 ± 7.6
Median (range)	64.5 (43 – 66)

REALM = Rapid Estimation of Adult Literacy in Medicine.

Study A01

Subject Disposition

- 12 subjects were enrolled, randomized, and received at least 1 dose
- 11 subjects completed the study
  - 1 subject was withdrawn due to "reactive hypertensive" after the second dose of *d*-amphetamine
    - not deemed a withdrawal caused by an adverse event

Study A01

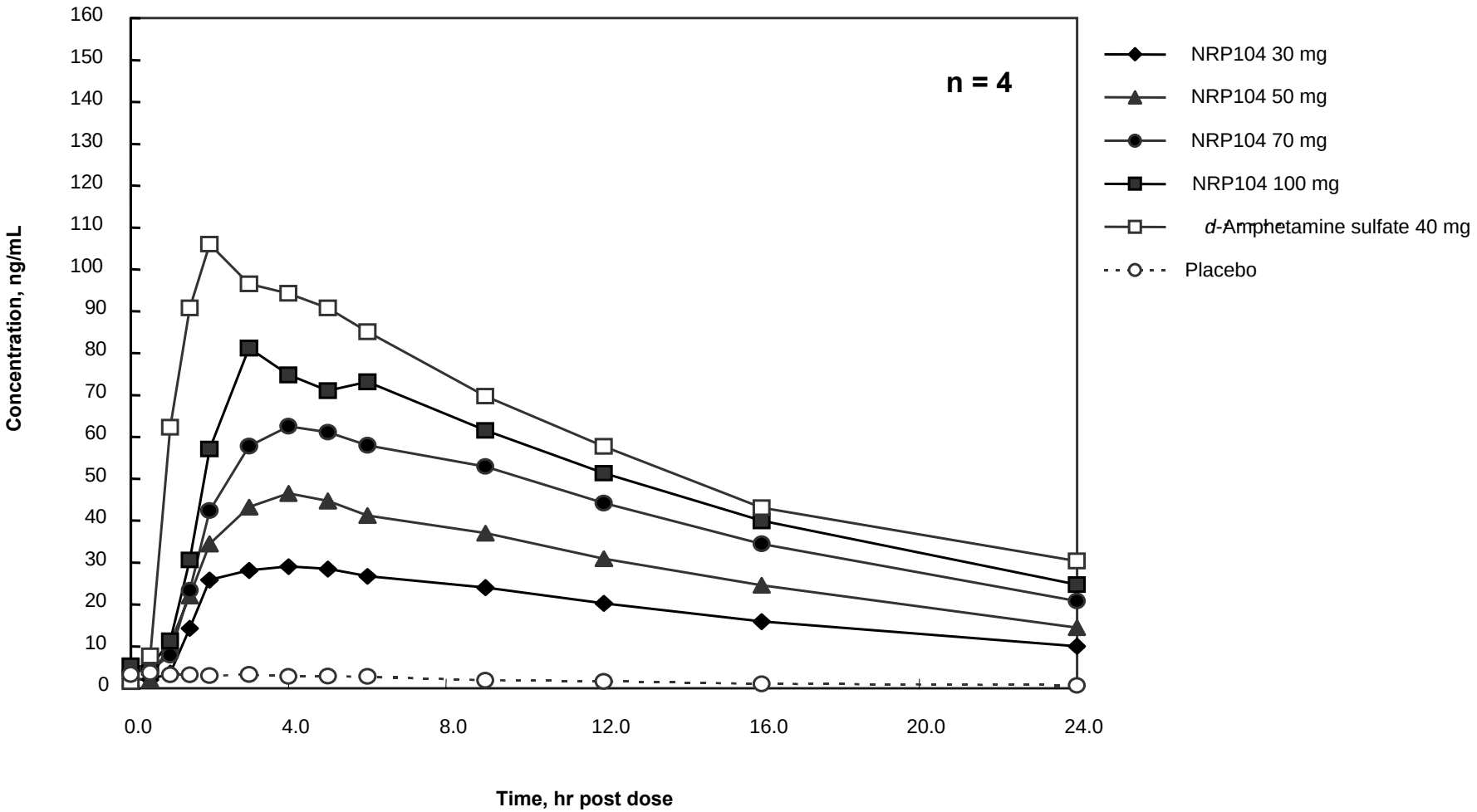
Cohort 1

- Four subjects completed
- NRP104
  - 30, 50, 70, 100 mg

PK Data: Cohort 1

Mean d-amphetamine Concentration-Time Plots

Study A01



Study A01

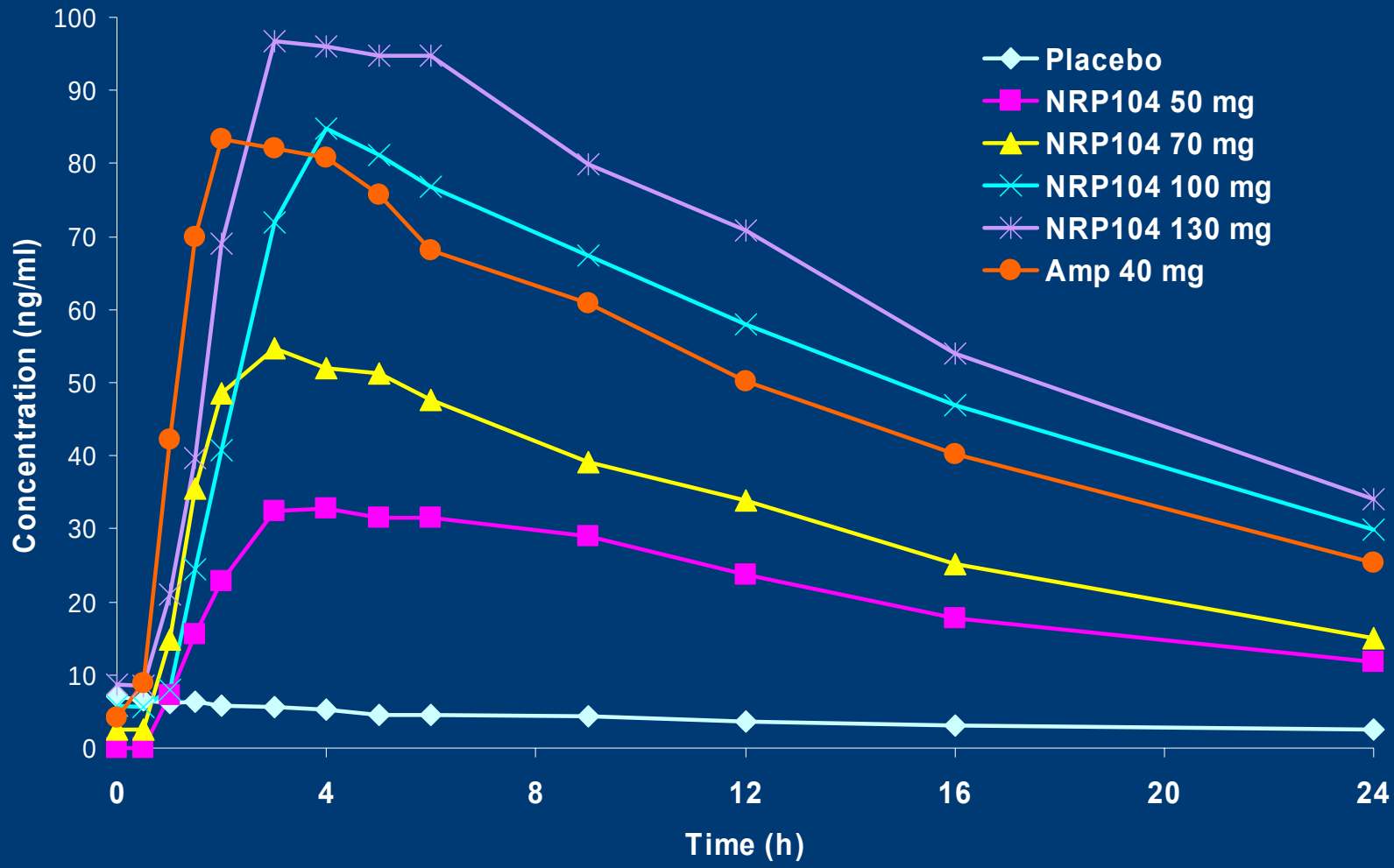
Cohort 2

- Four subjects completed
- NRP104
  - 50, 70, 100, 130 mg

Study A01

PK Data: Cohort 2

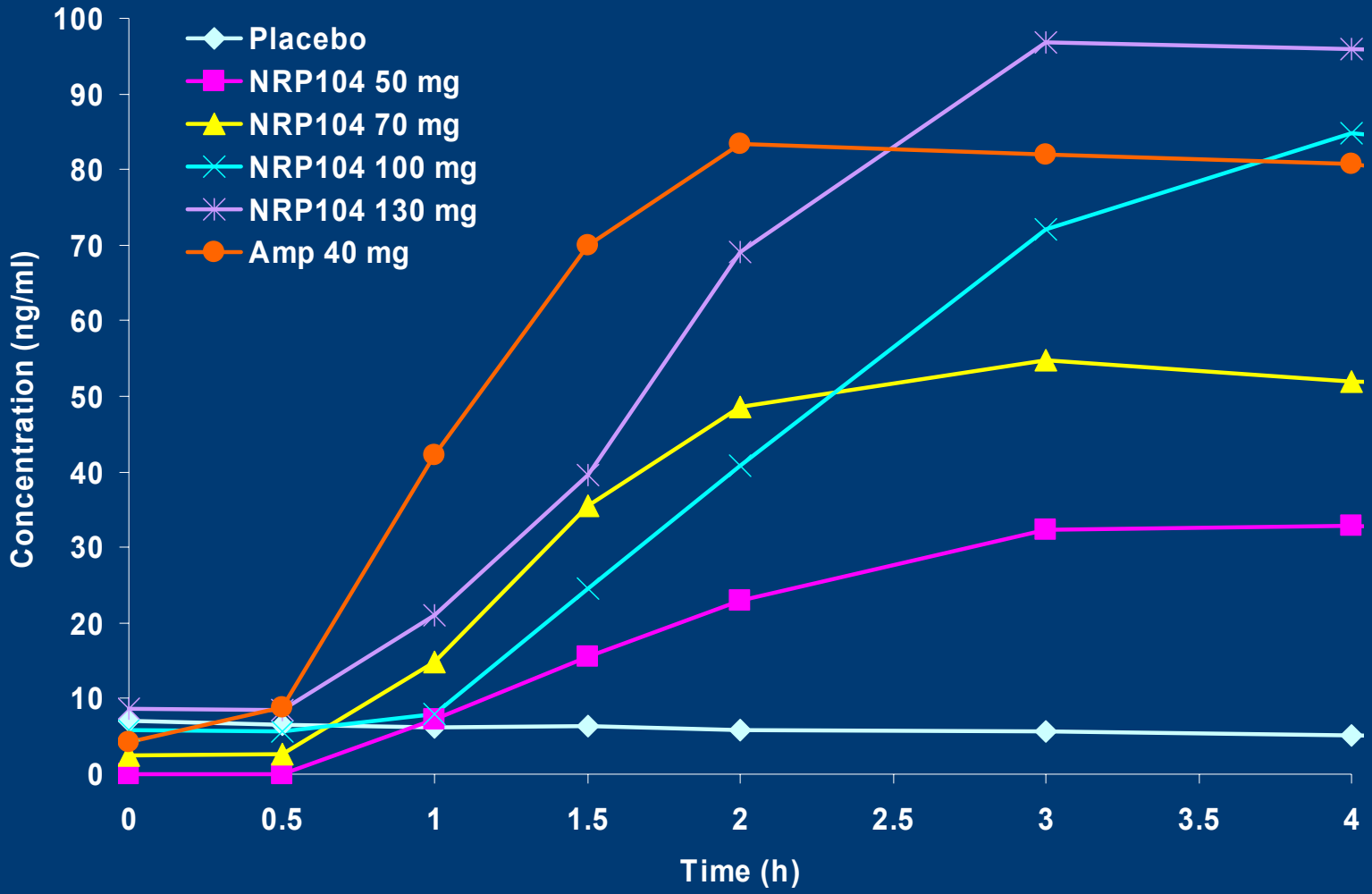
Mean d-amphetamine Concentration-Time Plots



Study A01

PK Data: Cohort 2

Mean d-amphetamine Concentration-Time Plots



Study A01

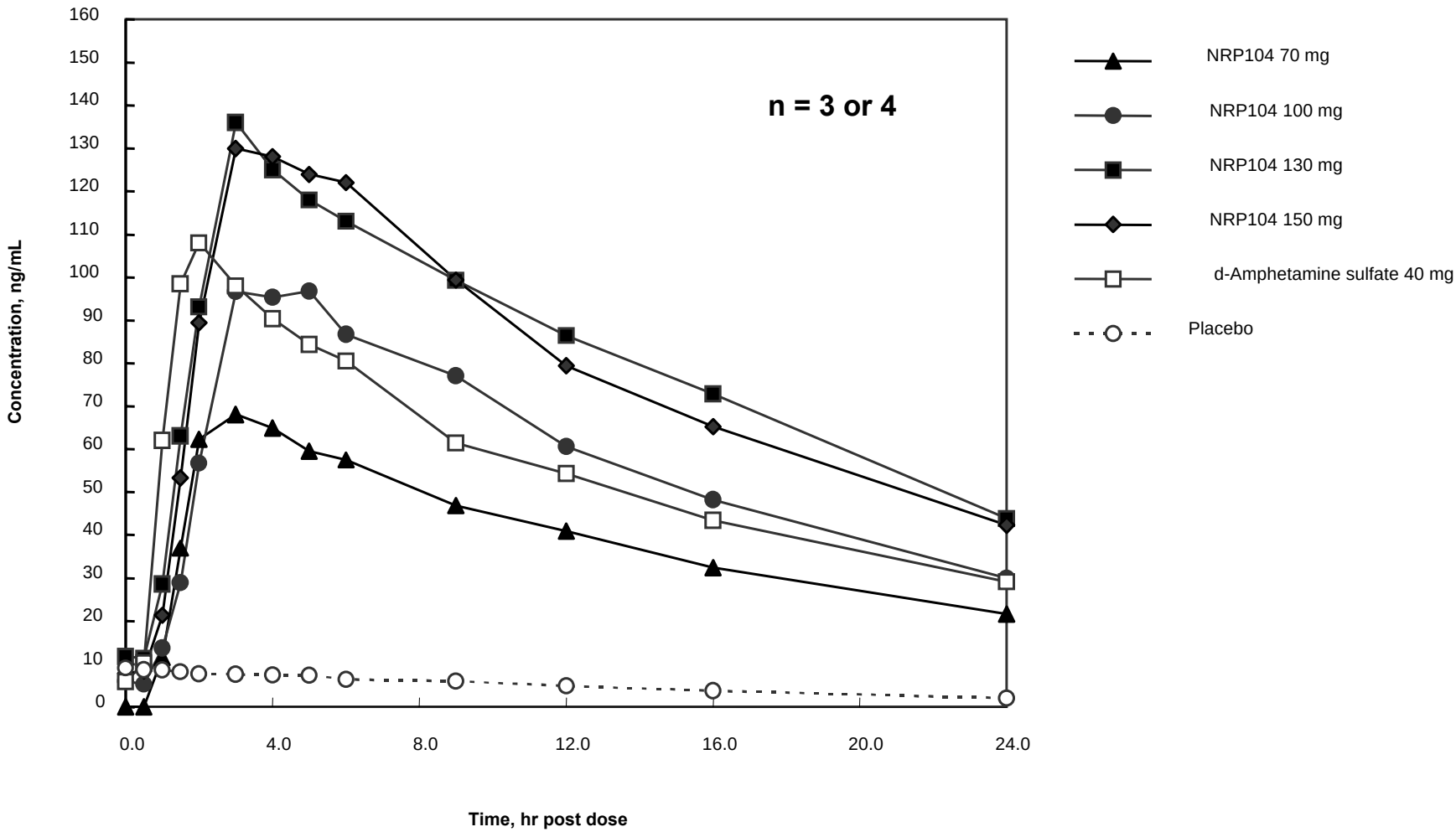
Cohort 3

- Three of four subjects completed
- NRP104
  - 70, 100, 130, 150 mg

PK Data: Cohort 3

Mean d-amphetamine Concentration-Time Plots

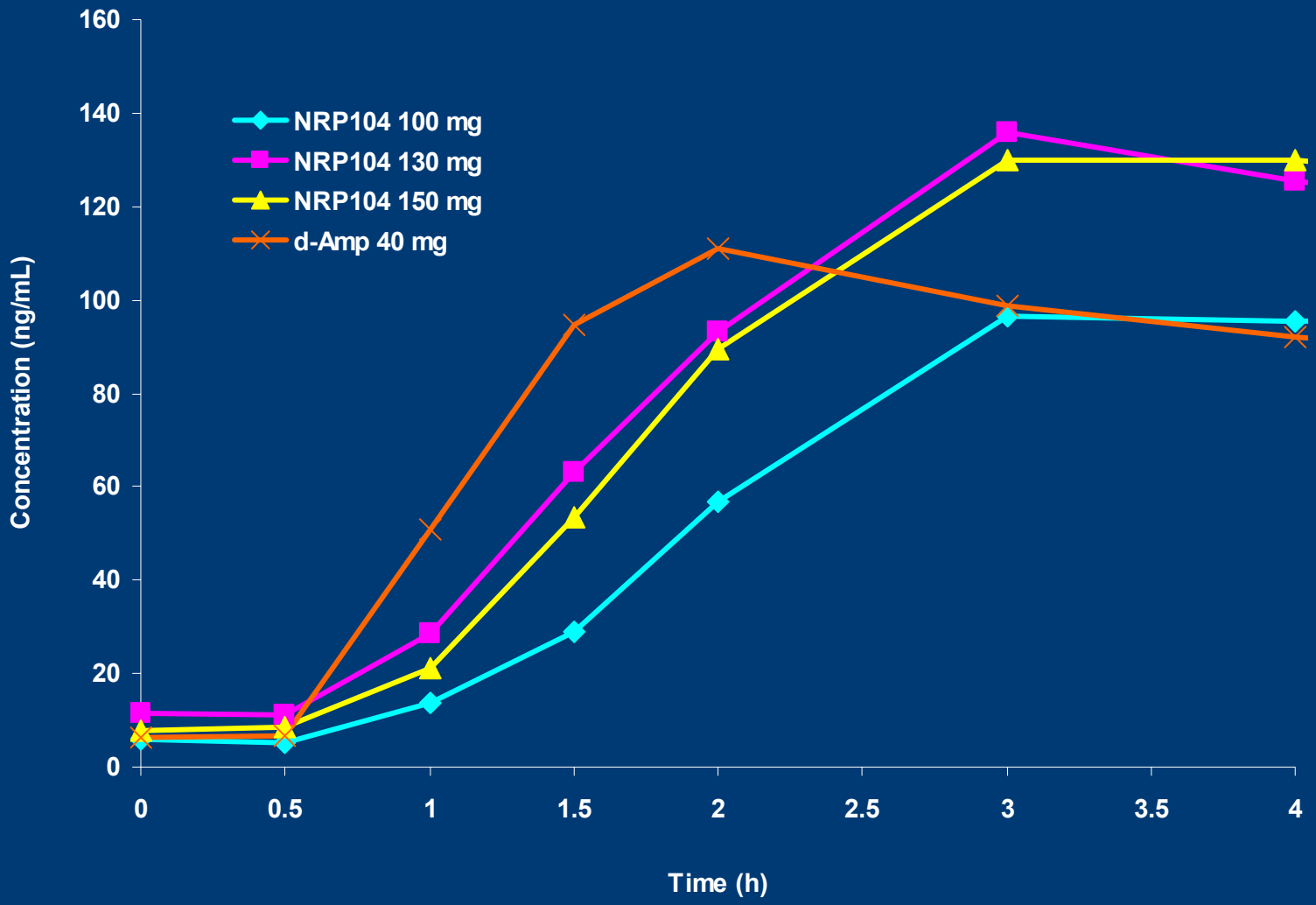
Study A01



Study A01

PK Data: Cohort 3

Mean d-amphetamine Concentration-Time Plots



A01 Summary

- Overall, *d*-amphetamine produced the expected subjective, behavioral, and cardiovascular effects that were distinguished from placebo
- Comparable doses of NRP104 tended to be less euphoric overall and more dysphoric with a later peak effect
- PK and PD data consistent with pre-clinical studies of rate limited hydrolysis
- Slower absorption phase
- Doses 50, 100, and 150 mg of NRP104 are safe and suitable for crossover study

Study A02

A Double- Blind Placebo- and Active-Controlled, Single-Dose Crossover Pharmacodynamic and Pharmacokinetic Study to Evaluate the Safety, Tolerability and Abuse Liability of Intravenously administered NRP104 25 mg and 50 mg in Healthy Adult Volunteers with Histories of Stimulant Abuse

Study A02

Study Design

- Phase II, randomized, single-center, double-blind dose run-up study
- Conducted at an in-patient residential unit
  - subjects confined to clinic for a minimum of 14 days
- Included a screening phase and an NRP104 dose run-up phase

Study A02

Subject Population

- ≥ 18 and ≤ 55 years of age
- Meet DSM-IV criteria for the diagnosis of substance abuse
- Have a history of IV drug use
- Not physically dependent on benzodiazepines, opiates, or alcohol
- Minimal reading level of grade 6, determined by the Rapid Estimation of Adult Literacy in Medicine (REALM) at investigator's discretion
- No presence of a severe learning difficulty or mental retardation

Study A02

Primary Objectives

- Investigate safety and abuse liability of a single intravenous (IV) dose of NRP104 in healthy adults with a history of stimulant abuse
- Compare safety profile with *d*-amphetamine and placebo
- Gather estimates of abuse liability

Study A02

Treatment

- Each subject received 1 single IV dose of NRP104, 1 single IV dose of *d*-amphetamine sulfate, and 1 placebo IV dose
- Minimum 2-day interval between dosing
- 3-way crossover drug administration

Cohort	Subject, n	NRP104	*d*-amphetamine	Placebo
1	3	25 mg	10 mg	Yes
2	9	50 mg	20 mg	Yes

Study A02

Assessments

- Abuse liability assessments
  - Drug Rating Questionnaire – Subject (DRQS)
  - Drug Rating Questionnaire – Observer (DRQO)
  - Treatment Enjoyment Assessment Questionnaire (TEAQ)
  - Addiction Research Center Inventory (ARCI) – to assess the degree of amphetamine like effects with Amphetamine and Benzedrine Group Subscales
- Cardiovascular assessments
  - systolic and diastolic blood pressure and pulse
- Safety assessments
  - adverse events monitored
- Pharmacokinetic assessments

Study A02

Subject Disposition

- 12 Subjects were enrolled, randomized, and received at least 1 dose
- All 12 subjects completed the study
- There were no protocol deviations on inclusion/exclusion criteria and no subjects were withdrawn due to protocol violations

Study A02

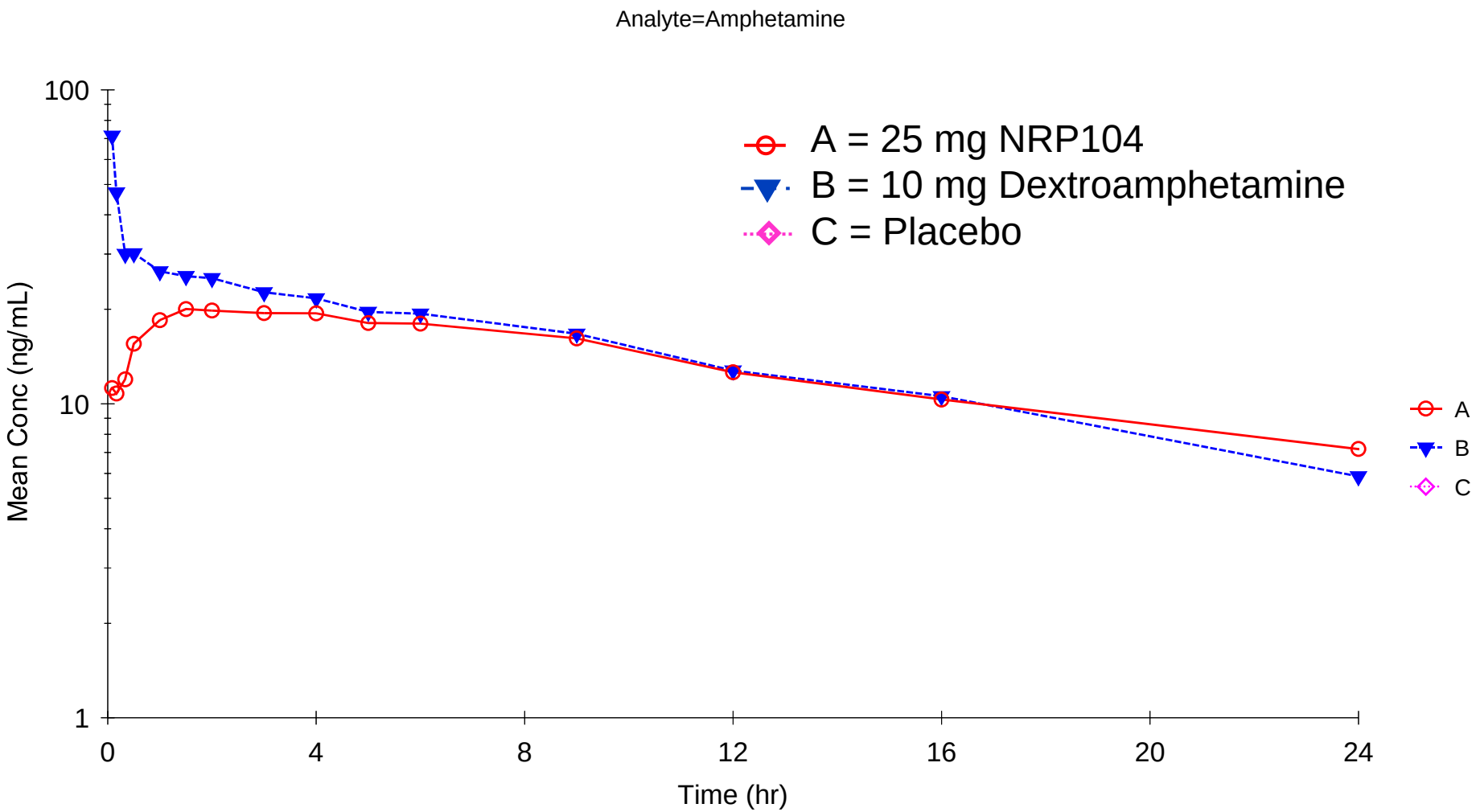
Demographics and Baseline Characteristics

Characteristic	N = 12
Age, years	
Mean ± SD	45.9 ± 3.3
Median (range)	45.5 (42 – 52)
Sex, n (%)	
Male	12 (100)
Race, n (%)	
White	1 (8)
Black	11 (92)
Height, cm	
Mean ± SD	176 ± 7.1
Median (range)	175.7 (159.5 – 185.4)
Weight, kg	
Mean ± SD	69.5 ± 10.3
Median (range)	68.8 (53.5 – 91.2)

PK Data: Cohort 1

Mean d-amphetamine Concentration-Time Plots in Semi-Logarithmic Scales

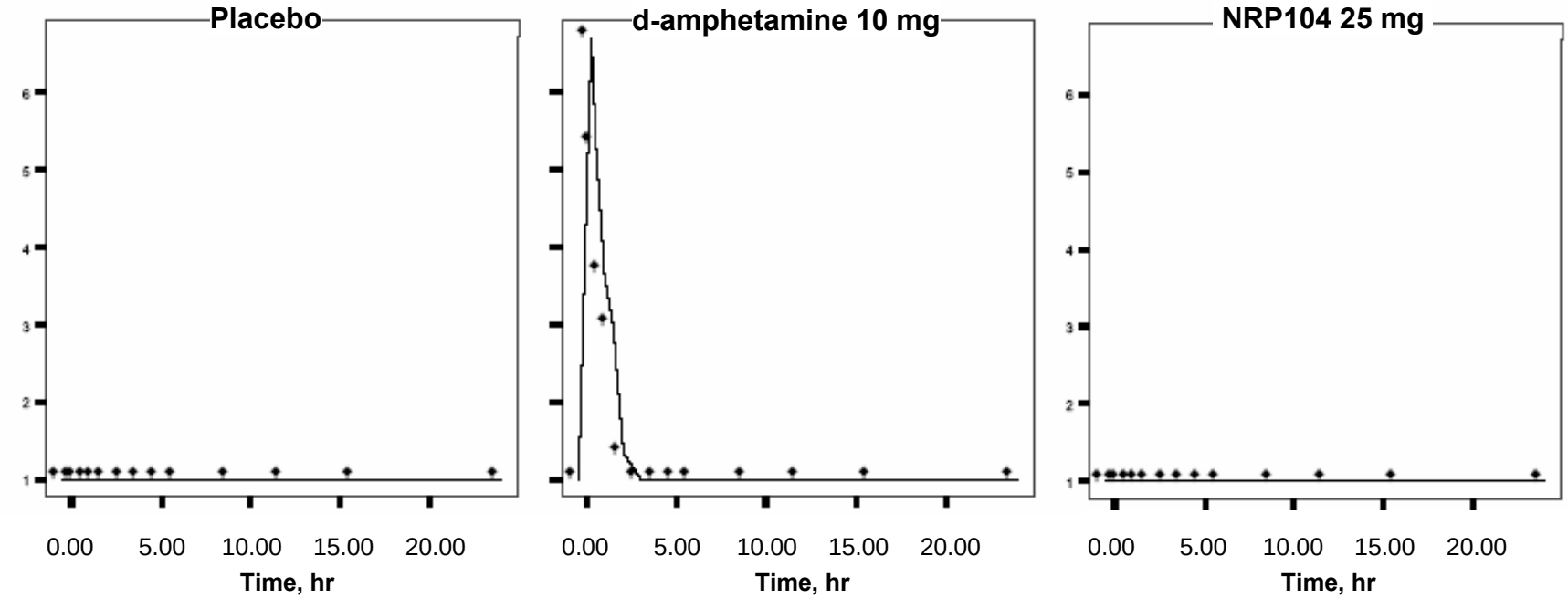
Study A02



Study A02

DRQS – Feel Drug Effect: Cohort 1

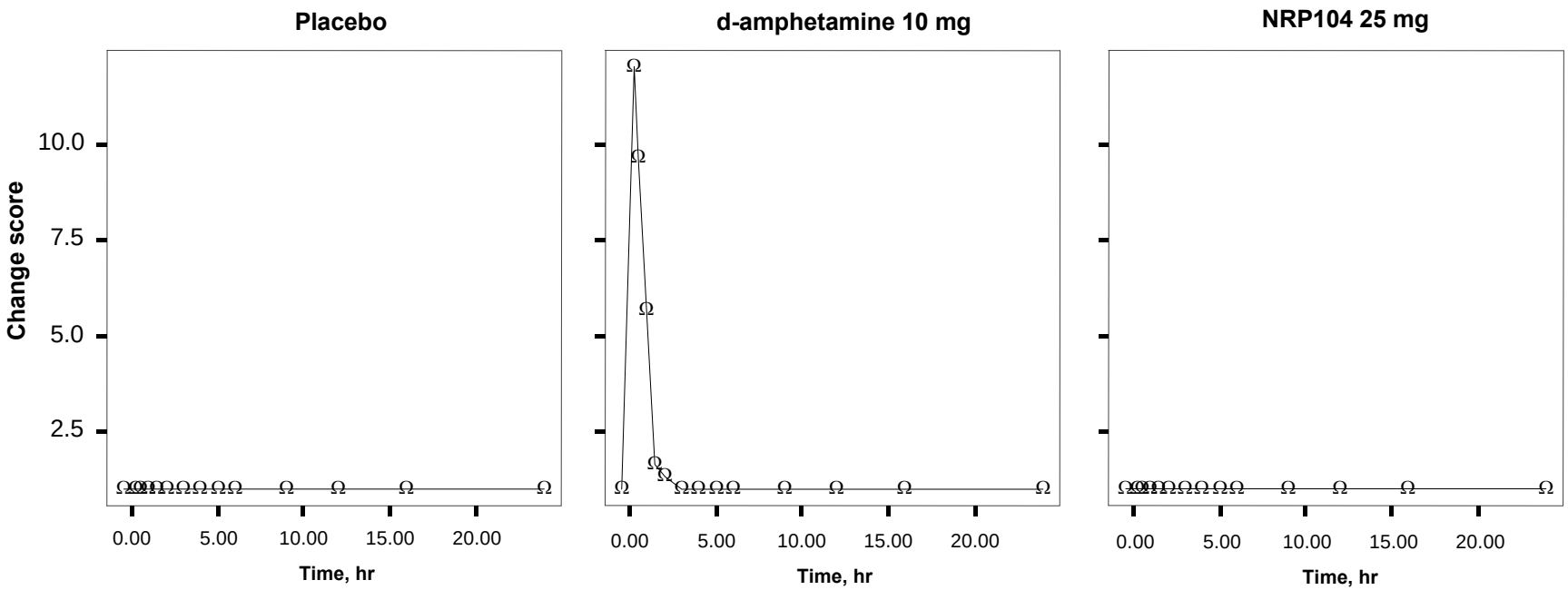
Do you feel a drug effect now?
Mean response



Study A02

DRQS – Liking: Cohort 1

Do you like the drug effect you are feeling now?
Mean Response



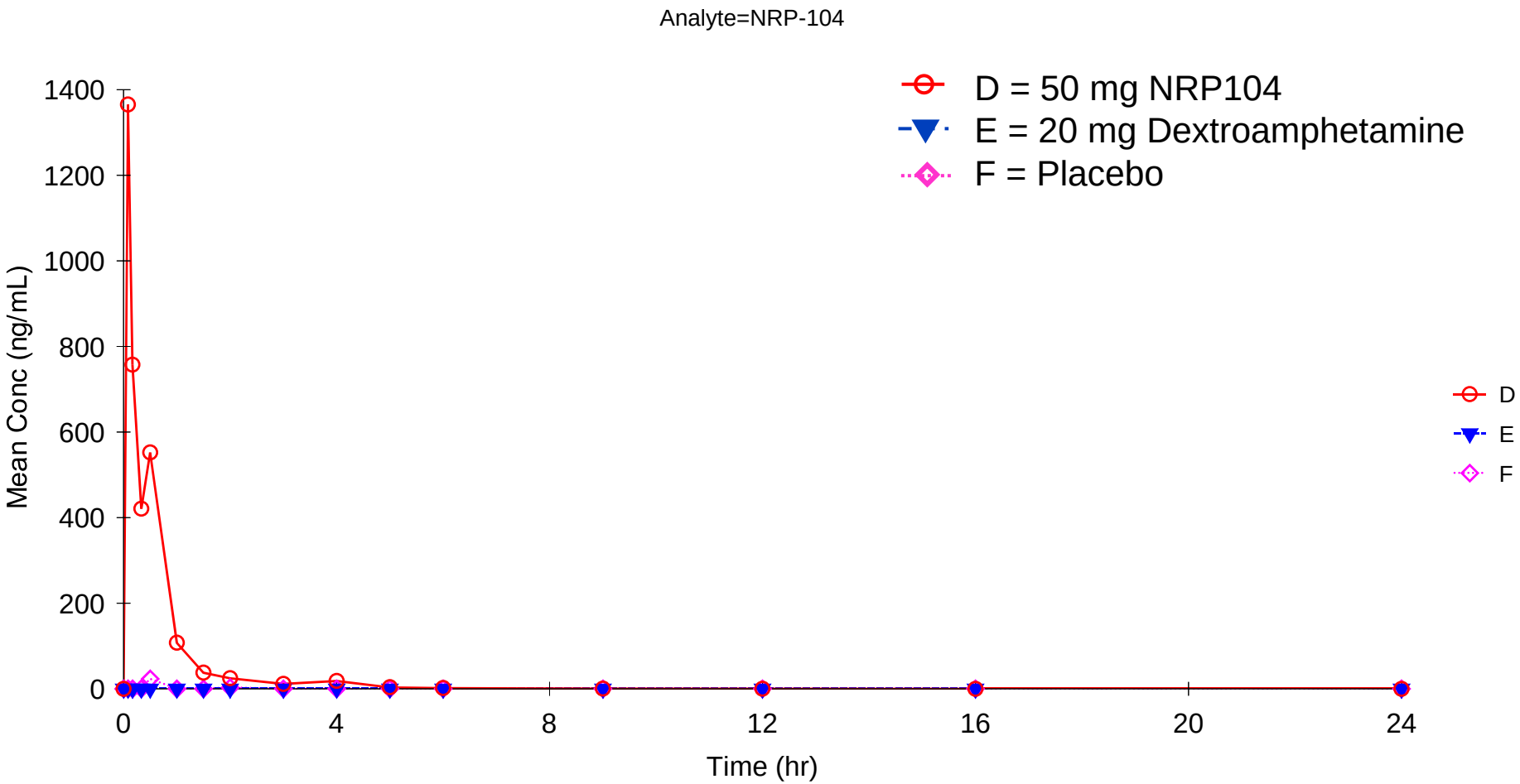
Study A02

Treatment Enjoyment Assessment Questionnaire: Cohort 1

Drug Chosen to Take Again		
	Subject	**Drug**
1	**1**	**d-amphetamine 10 mg**
2	**3**	**d-amphetamine 10 mg**
3	**4**	**d-amphetamine 10 mg**

Study A02

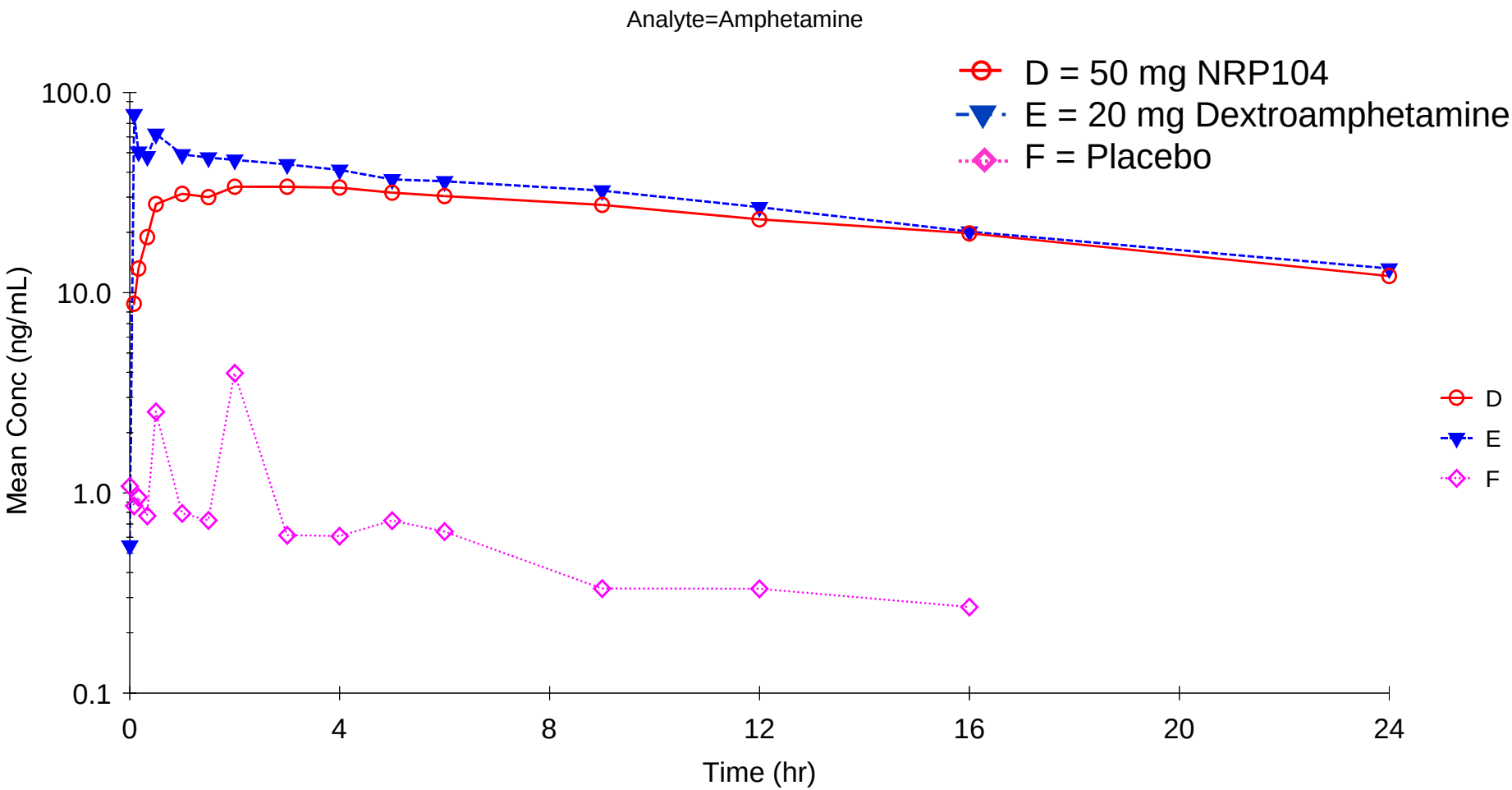
PK Data: Cohort 2
Mean NRP104 Concentration-Time Plots



PK Data: Cohort 2

Mean d-amphetamine Concentration-Time Plots
Semi-Logarithmic Scales

Study A02



Study A02

Pharmacokinetic Parameters for NRP104

Parameters	Mean ± SD	
	NRP104 25 mg (n = 3)	NRP104 50 mg (n = 9)
$T_{1/2}$, h	0.72 ± 0.09	1.25 ± 1.13
AUC_{0-24}, ng•hr/mL	281.9 ± 104.0	598.7 ± 232.9
C_{max}, ng/mL	1150 ± 710	1570 ± 779
T_{max}, hr	0.09 ± 0.01	0.18 ± 0.20

Study A02

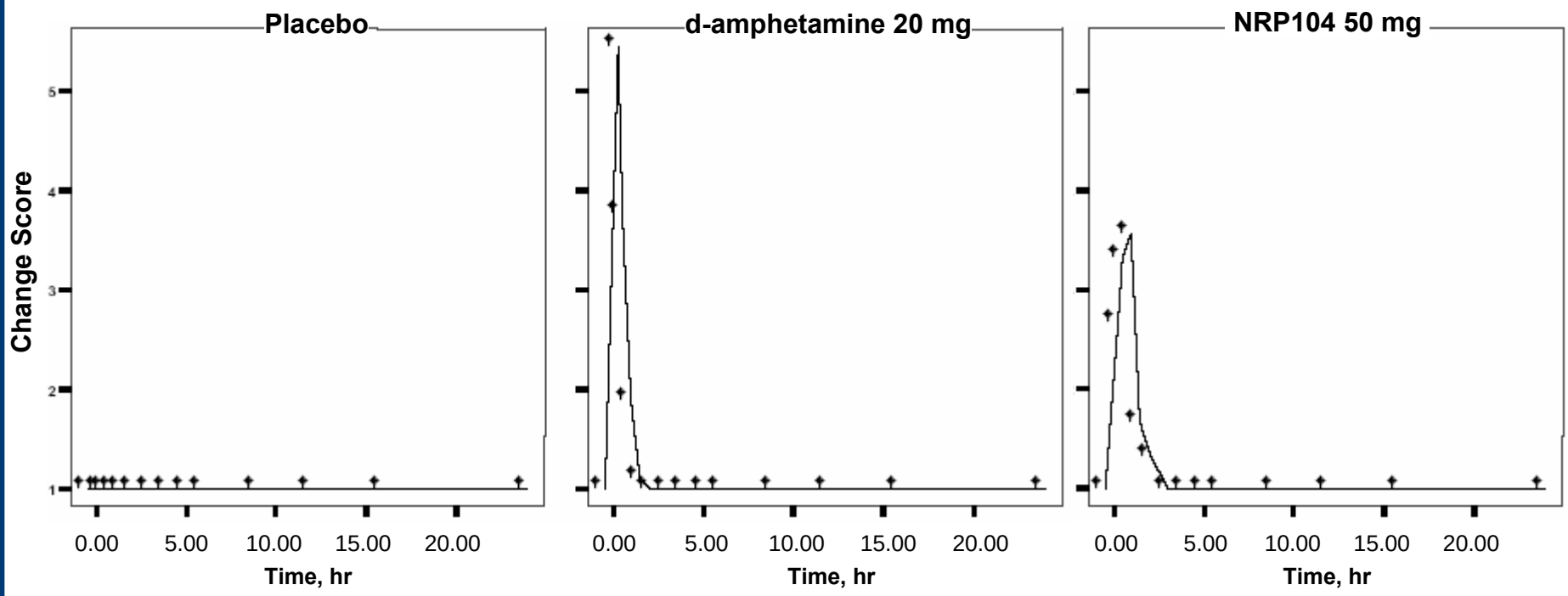
Pharmacokinetics Summary

- T_{max} of *d*-amphetamine after the administration of 25 or 50 mg NRP104 was substantially longer than after 10 or 20 mg *d*-amphetamine sulfate, respectively
- C_{max} of *d*-amphetamine after administration of 25 or 50 mg NRP104 was substantially lower (3 to 4 fold) than the C_{max} after administration of 10 or 20 mg *d*-amphetamine sulfate, respectively
- Within the first 4 hours, exposure to *d*-amphetamine from NRP104 was substantially lower than from *d*-amphetamine sulfate
- $T_{1/2}$ of intact NRP104 was approximately 1 hour after administration of either 25 or 50 mg of NRP105
  - indicating fast clearance of the intact compound

Study A02

DRQS – Feel Drug Effect: Cohort 2

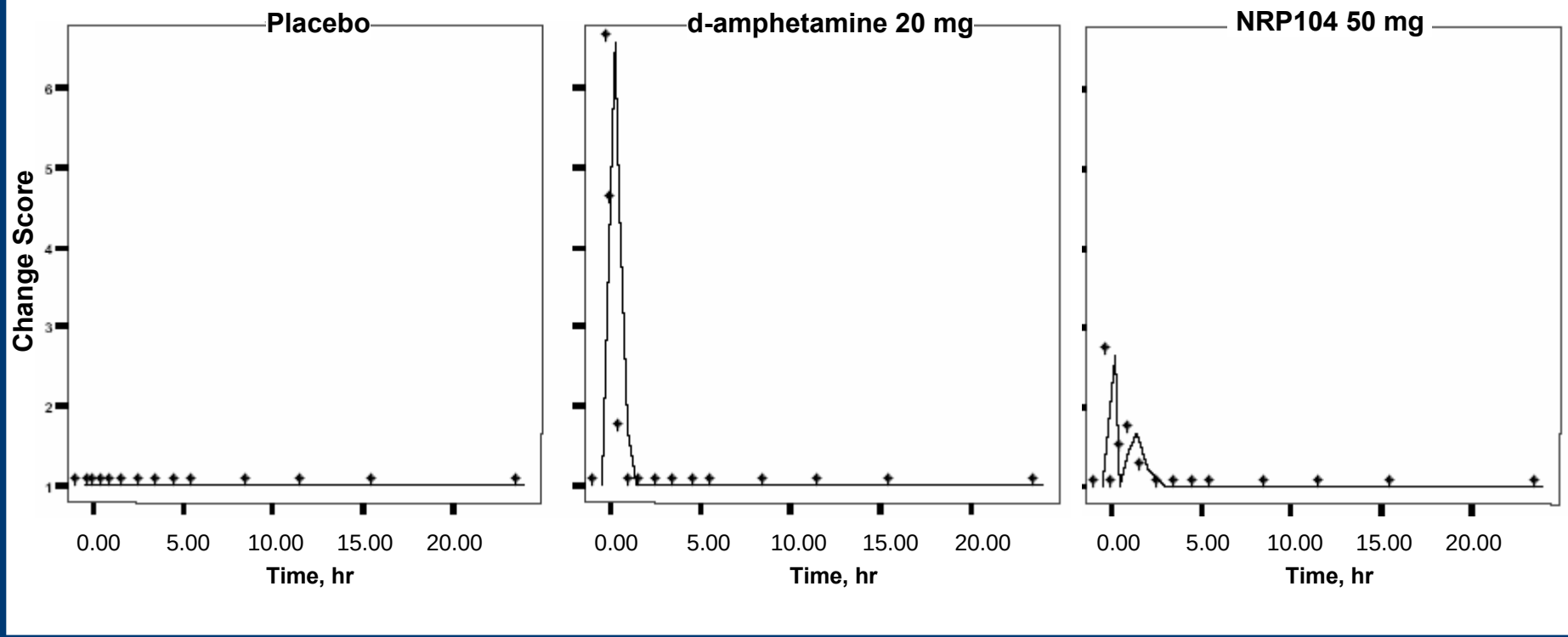
Do you feel a drug effect now?
Mean response



Study A02

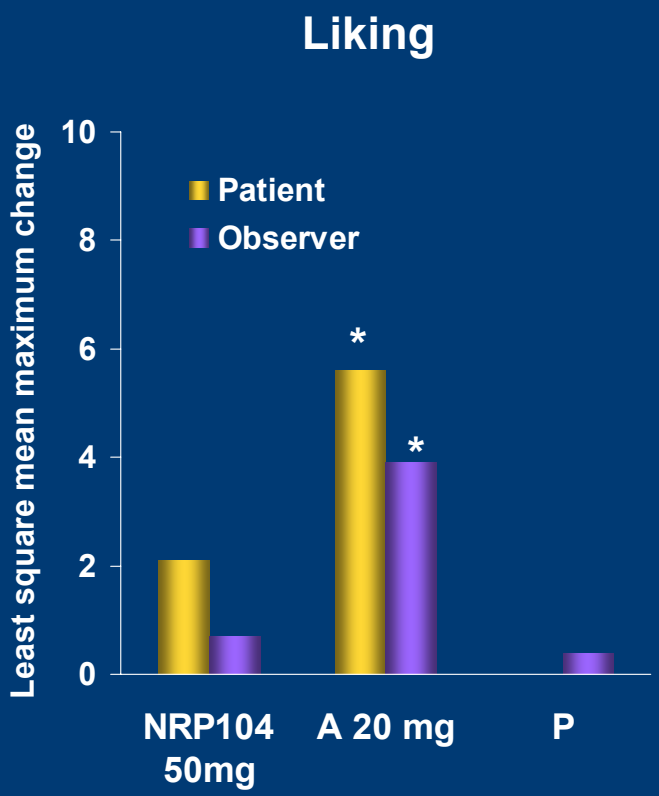
DRQS – Liking: Cohort 2

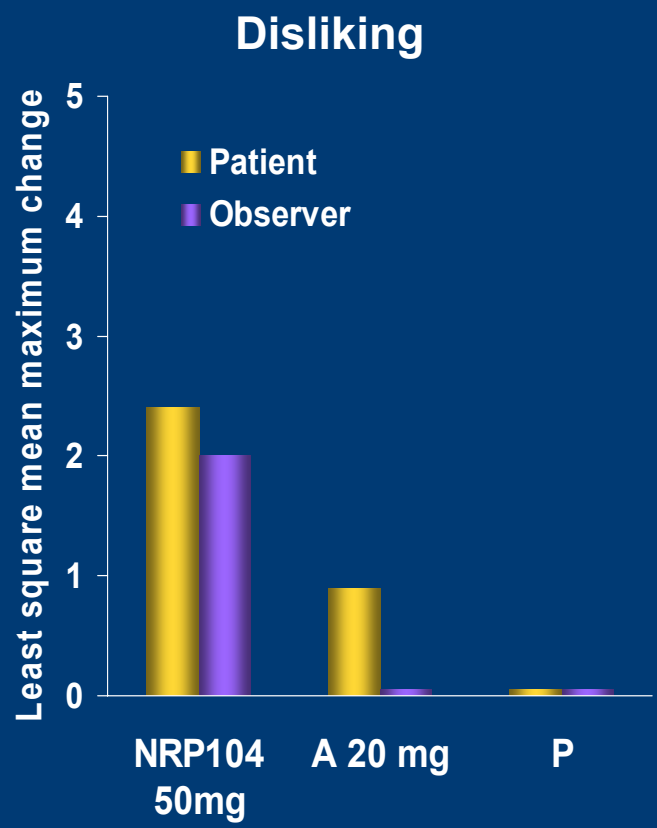
Do you like the drug effect you are feeling now?
Mean Response



Summary DRQ Measures Cohort 2 (n = 9)

Study A02



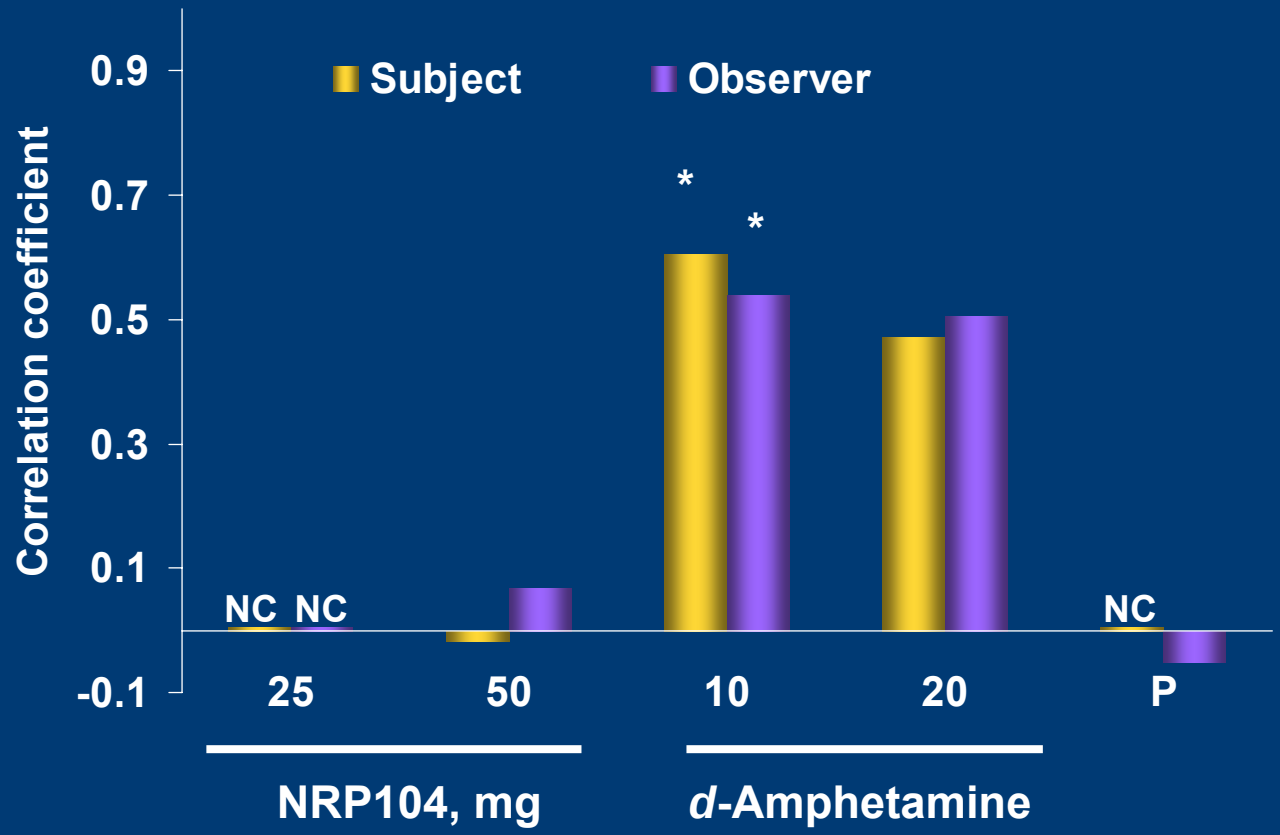


*$P < 0.05$ compared with placebo.

A = *d*-Amphetamine; P = Placebo.

Correlation Between Mean *d*-Amphetamine Plasma Levels and the Liking Measures

Study A02



*$P < 0.05$.

NC = Not calculable; P = Placebo.

Study A02

Treatment Enjoyment Questionnaire: Cohort 2

Drug Chosen to Take Again		
	Subject	**Drug**
1	2	None of the treatments
2	5	d-amphetamine 20 mg
3	6	d-amphetamine 20 mg
4	7	None of the treatments
5	8	NRP104 50 mg
6	9	d-amphetamine 20 mg
7	10	d-amphetamine 20 mg
8	11	d-amphetamine 20 mg
9	12	d-amphetamine 20 mg

A02 Conclusions

- In this IV abuse liability study, NRP104 had less euphoric effects compared to equal doses of *d*-amphetamine sulfate
- NRP104 was significantly less reinforcing than *d*-amphetamine sulfate as evidenced by the majority of the subjects choosing not to take lisdexamfetamine dimesylate again, in the Treatment Enjoyment Assessment Questionnaire administered at the end of the study
- This reinforcement profile is consistent with a 2 to 4 fold reduction in peak plasma amphetamine concentration (Cmax) and and increased time to peak concentration (Tmax) of approximately 2 hours after intravenous administration

Study A03

A Double-Blind, Randomized, Placebo and Active-Controlled, Six-Period Crossover Study to Evaluate the Likeability, Safety, and Abuse Liability of NRP 104 in Healthy Adult Volunteers with Histories of Stimulant Abuse (NRP104.A03)

Design and Methods

- 30 male and 6 female stimulant abusers
- Six 6X6 balanced Latin squares for crossover design
- Primary variable is maximum score on VAS scale to item “ How much do you like the drug effects you are feeling now?”

Drug and doses given orally

- Placebo
- 40 mg d-amphetamine (Schedule II)
- 200 mg diethylpropion (Schedule IV)
  - Pro-drug
  - Subjective and behavioral effects comparable to d-amphetamine 40 mg
- Lisdexamfetamine
  - 50 mg (base = d-amp 20 mg)
  - 100 mg (base = d-amp 40 mg)
  - 150 mg (base = d-amp 60 mg)

Primary Endpoint - Peak Liking Score

Dependent Variable: Do you like the drug effect you are feeling now?

Drug (I)	Drug (J)	Mean Difference (I – J)	Std. Error	Significance	95% Conf. Interval (Lower Bound)
d-amphetamine 40 mg	Placebo	4.53*	1.148	< 0.001	1.94
diethylpropion 200 mg	Placebo	4.03*	1.148	0.001	1.44
LDX 100 mg	Placebo	2.14	1.148	0.113	-0.45

Based on observed means

* - The mean difference is significant at the 0.05 level

Primary Endpoint: Peak Liking Score

Dependent Variable: Do you like the drug effect you are feeling now?

Drug (I)	Drug (J)	Mean Difference (I – J)	Std. Error	Significance	95% Conf. Interval (Lower Bound)
LDX 50 mg	Placebo	1.97	1.148	0.148	-0.61
LDX 100 mg	Placebo	2.14	1.148	0.113	-0.45
LDX 150 mg	Placebo	6.06*	1.148	0.001	3.47

Based on observed means

*** - The mean difference is significant at the 0.05 level**

Peak Liking Scores

- d-amphetamine and diethylpropion
  - 1.5 to 2 hours
- NRP104
  - 3 to 4 hours

Top Line Results

- LDX attenuates onset and intensity of liking effects
- Liking effects of LDX 50 and 100 mg not significantly different than placebo
- Liking effects of LDX 150 mg greater than placebo but similar to d-amphetamine and diethylpropion; however, mean peak effect delayed

Top Line Results

- Rate-limited hydrolysis of LDX in humans
- Pro-drug attenuates onset and intensity of amphetamine-like effects
- Attenuated Liking Scale scores
  - Less reinforcing than equivalent d-amphetamine or diethylpropion
  - Contribute to lesser abuse potential