

CENTER FOR DRUG EVALUATION AND RESEARCH

SPECIAL INTEREST TOPIC

TITLE: IND 38,108 PHASE IV PROTOCOL

DATE: JUNE 27, 1997

ORIGINAL
N044 PC

*Renew Am
7/07/97*

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June 27, 1997

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Center for Drug Evaluation and Research
Food and Drug Administration
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RE: IND 38,108
Serial number 044
New Protocol (revised amendment)



Dear Dr. Sobel:

Reference is made to our teleconferences of June 23 and 25. Reference is also made to our protocol submitted June 16, 1997 (serial number 042). During the June 23 teleconference we reached agreement on the scope and time points of testing in this protocol; you indicated that the tests and time points in our June 13 protocol version were acceptable. During the teleconference we agreed with Drs. Lutwak and Stadel to change the wording of exclusion criteria number 9 to make it less restrictive. We also agreed with Drs. Pian and Nevius to change several items in the statistical section (pages 22, 23, and 27).

During the June 25 teleconference, you indicated that the number of patients assigned to the dexfenfluramine and placebo arms of the study should be increased from n=160 per group to n=240 per group. You indicated that the fluoxetine arm could be retained, at our discretion, and that the number of patients entered into that arm could be: retained at n=160, increased, decreased, or indeed dropped completely from the study. We have elected to retain this arm at n=160.

The protocol has been modified to include all the above changes and is enclosed. We feel we have reached closure on this protocol design. We will submit this protocol to the sites for IRB submission and will begin enrolling patients as soon as feasible.

If you have any questions, I can be reached at (617) 861-8444 extension 417.

Regards,

Sonja Bloar

Sonja Barton Loar, Pharm. D.
Vice President, Regulatory & Scientific Affairs

REVIEWS COMPLETED		
CSO ACTION:		
<input checked="" type="checkbox"/> LETTER	<input type="checkbox"/> N.A.I.	<input type="checkbox"/> MEMO
<i>MSH</i>		<i>7-17-97</i>
CSO INITIALS		DATE



**INTERNEURON PHARMACEUTICALS, INC.
LEXINGTON, MASS 02173**

CONFIDENTIAL

Clinical Study Protocol

TITLE OF STUDY:

**THE EFFECTS OF 12 AND 24 MONTHS OF DEXFENFLURAMINE
TREATMENT ON NEUROPSYCHOLOGICAL FUNCTION
IN OBESE PATIENTS**

12 / 02 / 96
M D Y
DATE OF ISSUE

06 / 27 / 97
M D Y
DATE OF AMENDMENT #1

PROTOCOL NO:

IP96-007
Amendment No. 1

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I. INTRODUCTION

Nineteen double-blind, placebo-controlled studies of 3, 6, or 12 months duration, involving over 1,500 obese outpatients have confirmed the efficacy and safety of dexfenfluramine (15 mg *b.i.d.*, p.o.) for inducing weight reduction in heterogeneous populations of obese patients. Throughout the studies, in addition to receiving dexfenfluramine (or placebo), the patients were also prescribed a diet (except for one study).

Presently, dexfenfluramine is marketed worldwide in approximately 80 countries. Development of dexfenfluramine was based on the fact that: (1) it constitutes the pharmacologically active half of racemic d,l-fenfluramine, and (2) the results of animal and human studies suggested that a similar degree of appetite-suppressant activity with improved tolerability could be obtained when the dose of dexfenfluramine was half that of racemic fenfluramine. Since the usual effective dose of Pondimin® (d,l-fenfluramine) is 60 mg daily (20 mg, *t.i.d.*), a dose of 30 mg daily of dexfenfluramine was readily adopted in placebo-controlled trials and found to be clinically well-tolerated and pharmacologically active in the reduction of body weight. This was confirmed in a dose-ranging trial which compared 5 mg *b.i.d.*, 15 mg *b.i.d.*, 30 mg *b.i.d.* versus placebo. It is this dose, *i.e.* 30 mg of dexfenfluramine daily, that is widely recommended for treatment of obese patients.

The reduction in brain serotonin (5-HT) and 5-hydroxyindoleacetic acid (5-HIAA) content following the administration of high doses, up to 30 times the clinical dose, of fenfluramine or dexfenfluramine to animals has been known for over 20 years. These findings vary markedly across species and by route and regimen of dosing. Some investigators have interpreted the reduced brain indole levels and the correlated observations of diminished visualization of neurons by 5-HT immunohistochemistry and reduced 5-HT transporter number as surrogate indicators of neurotoxicity. It is this interpretation that has been the subject of years of contentious debate. Critical to the issue of neurotoxicity in animals is whether or not acute or long-lasting behavioral or functional deficits are observed with prolonged treatment. In this regard, the subchronic (30-38 days) and chronic (>6 months) administration of dexfenfluramine or fenfluramine fail to produce any significant or persistent adverse functional or behavioral effects in rats. Sensitive memory processes in aged rats, for example, are unaffected by subchronic and chronic dexfenfluramine (0.6-1.2 mg/kg/day, po) administration. Furthermore, the subchronic and chronic administration of dexfenfluramine (0.2-0.6 mg/kg/day, po) has been found to actually restore the normal hormonal response to stress and to maintain the NK and T cell arms of the immune system of aged rats at youthful levels.

Fenfluramine and dexfenfluramine have been widely used clinically with an estimated 30 million patients treated during the last 20 years. No epidemiological signal of adverse behavioral or cognitive effects has emerged. Specifically for dexfenfluramine, a comprehensive medical and safety review of neurologic, psychometric, behavioral or cognitive test data from 17 controlled clinical trials, of 10 years of post-marketing spontaneous reports and of 55 reports in the published literature was conducted to evaluate the human risk for adverse psychological, neurologic or psychiatric effects associated with dexfenfluramine treatment. The ratings were collected in therapeutic trials involving obese patients, or pilot therapeutic trials in other disorders, for the purpose of assessing the potential for CNS consequences of dexfenfluramine treatment. These studies are substantial in terms of the number of patients investigated, the dexfenfluramine dose and duration of treatment, and the outcome measures employed. The neuropsychological tests and rating instruments used are well established in clinical neuropsychopharmacology and are capable of detecting clinically meaningful changes in response to drug exposure. Many of these same tests are recommended by WHO or NIMH for evaluating neurotoxicologic effects of human exposure to environmental or industrial chemicals. The review focused on human behaviors that serotonin is postulated to modulate (*i.e.*, appetite, mood, suicidal ideation, attention, concentration, memory) or on neurologic signs.

The results of this review of clinical findings indicate that, at the dose recommended for the treatment of obesity, dexfenfluramine is safe and well tolerated. There were no findings on any of the behavioral, cognitive or neuropsychological tests used that indicated adverse behavioral or cognitive effects. These findings are in concert with clinical experience comprised of an estimated 10 million patient exposures to dexfenfluramine.

Nevertheless the behavioral and neuropsychological effects of long-term (*i.e.*, one year or greater) use of any serotonergic psychotropic drug, including dexfenfluramine, have not been systematically examined across psychopathologic and cognitive domains with comprehensive serial testing in a single patient sample. The objective of this study is to describe the neuropsychological effects of prolonged 5-HT reuptake blockade and release in obese outpatients.

II. OBJECTIVES OF STUDY

The primary objective of this study is to determine the effect, if any, of dexfenfluramine (15 mg given *b.i.d.*) compared to both fluoxetine (60 mg/day, the standard dose employed in obesity studies) and placebo on behavioral and neuropsychological parameters in obese outpatients.

The secondary objectives of the study are to determine the reversibility of any observed changes in neuropsychological test findings and to examine the efficacy of dexfenfluramine for weight loss and maintenance over a 2-year treatment duration.

III. DESIGN AND RATIONALE

A. Basic Design Characteristics

The study is a multi-center, double-blind, randomized, placebo-controlled, placebo-substitution design involving 12 months of active or placebo treatment and 12 months of placebo-controlled post-treatment follow-up using a randomized placebo-substitution design. Tests to measure behavioral or neuropsychological function will be administered during double-blind treatment and double-blind, placebo-substitution post-treatment follow-up phases.

The general design is shown in the study schematic, Figure 1.

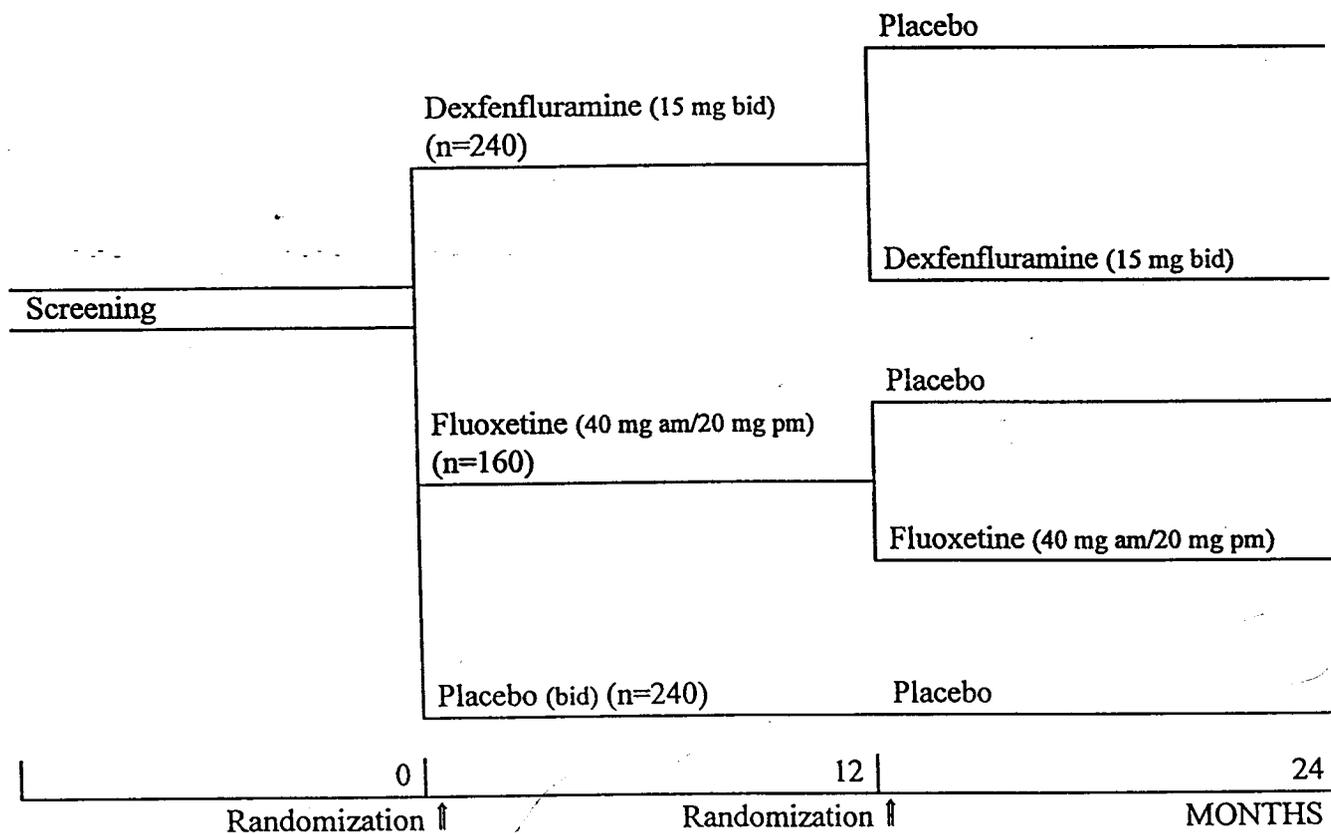
Obese patients with BMI values of ≥ 27 kg/m² with comorbid hypertension or NIDDM, or BMI values of ≥ 30 kg/m² with or without a comorbid illness will be randomized to receive either dexfenfluramine (15 mg *b.i.d.*), fluoxetine (40 mg A.M./20 mg P.M.) or placebo (*b.i.d.*) for a period of 12 months. Patients initially assigned to dexfenfluramine or fluoxetine treatment who complete 12 months of treatment will then be randomly assigned to continue the same active treatment or to receive placebo for an additional 12 months. Patients initially assigned to placebo treatment will continue on placebo for an additional 12 months. A total of 640 patients will be entered into the study. Two hundred forty (240) patients each will be randomized to receive dexfenfluramine, or placebo, and one hundred sixty (160) patients will be randomized to receive fluoxetine.

A battery of behavioral and neuropsychological tests will be administered at baseline and repeated periodically through the study. The tests, and the timing of their administration, are shown in the Study Flow Chart (page 10). Tests have been selected for their validity in assessing relevant neuropsychological functions, as well as for the availability of, or ease of creating, alternate forms. Testing has been scheduled so that patients will receive identical alternate forms at baseline and at the most important end points (12 months and 24 months) of the study.

B. Study Rationale

Decrements in central serotonergic function are postulated to increase the risk of depressive symptoms, hostility, impulsive behavior and suicide, and to decrease cognitive function. The selected tests provide a careful, double-blind assessment of each of these behavioral and cognitive domains at baseline, during active treatment, and for 12 months after treatment discontinuation. The primary endpoint will be behavioral or cognitive test results following 12 months of treatment compared to baseline. If a change is observed, the placebo-substitution follow-up period will evaluate the reversibility of the effect and the time course of return to baseline function. The long-term effects on behavioral or cognitive function of blocking 5-HT reuptake and promoting 5-HT release have never been systematically studied for any serotonergic agent.

FIGURE 1: STUDY SCHEMATIC



There are no animal or clinical data that suggest a specific behavioral or neuropsychologic effect of long-term dexfenfluramine treatment. In this context it is not appropriate to designate a specific behavioral or neuropsychological domain as the primary outcome measure for hypothesis testing or for sample size estimates. Therefore, tests have been selected and grouped to evaluate the two major areas postulated to be affected by diminished serotonergic function, Behavioral Domains and Neuropsychological Domains. The domains and tests within each of these are shown in Table 1.

In order to maximize the sensitivity of the experiment to detect either changes in means or association with infrequent events, the data from the primary behavioral or neuropsychological domains will be analyzed by a variety of methods, as described in Section VIII.B, Statistical Analysis. Changes in behavioral or neuropsychological tests will be correlated against covariates, e.g. baseline weight and weight loss, to determine if the effects are related to drug treatment or are secondary to other factors. Evaluations will also include univariate analyses with appropriate adjustments for covariates. The power of this study to detect clinically meaningful changes is $\geq 85\%$; this estimate is described in Section VIII.B.

In order to distinguish between effects due to (a) adaptive changes in serotonergic neurotransmission that would occur with any serotonergic agonist and (b) those that are unique to dexfenfluramine, we have included an active treatment comparison group. This group will be treated with fluoxetine, a serotonergic agent with documented ability to induce, but not maintain, weight loss in obese outpatients, but with a somewhat different mechanism of action. Because fluoxetine acts primarily by blocking serotonin reuptake, while dexfenfluramine acts to both block reuptake and stimulate serotonin release, data from this study will provide valuable information about the potential differences between these mechanisms of action on behavioral and neuropsychological - as well as weight loss - effects.

Table 1: Dexfenfluramine Longitudinal Study: Assessment Domains

Behavioral Domains:	
1. Mood/Affect	Beck Depression Inventory Beck Hopelessness Scale
2. Hostility/Impulsivity	Buss-Durkee Hostility Inventory Brown-Goodwin Aggression Scale Barratt Impulsiveness Scale
3. Suicidality	Beck Suicide Ideation Scale Suicide History - Short Term *Suicide Attempt Lethality Rating (*for any attempts during study)
4. Appetite and Eating Behavior	Questionnaire on Eating and Weight Patterns Stunkard Eating Inventory
5. Sexual Function	Rush Sexual Function Scale
Neuropsychological Domains:	
1. Motor Speed/Reaction Time	Finger Tapping Test Choice Reaction Time
2. Attention/Concentration	Continuous Performance Test Stroop Color/Word Test
3. Verbal Memory	Buschke Selective Reminding Test Verbal Paired Associates
4. Non-Verbal Memory	Benton Visual Retention Test (Administration D) Visual (Faces) Paired Associates
5. Inhibitory Control	Time Estimation Go-No Go Task
6. Executive Functioning	Logical Reasoning Verbal Fluency
7. Subjective Cognitive Function	Cognitive Failure 25

C. Drop Outs

Patients who drop out at any point in the study will be contacted for a termination assessment - provided that it has been at least one month since their most recent assessment - and will be given their final end-point assessment. These termination assessments will then be employed in an intent-to-treat analysis using the last observation carried forward method.

IV. DRUGS/DOSAGES

A. Identification and Description of Investigational Drug

Study formulations will include dexfenfluramine hydrochloride (15 mg capsules), fluoxetine (20mg capsules) and matching placebo for each active treatment group.

The capsules will be packaged and shipped to the study site.

Packaging: Each patient will receive two bottles of study medication each month. Bottle A (red label) will contain 70 capsules and Bottle B (yellow label) will contain 35 capsules.

Labeling: A three-part, tear off label will be attached to each patient's bottles of capsules. Each label will bear the following information:

1. the name and address of sponsor,
2. the Investigational New Drug statement,
3. the study number (IP96-007),
4. the directions for use,
5. the storage instructions, and
6. a description of the actual test article (strength and lot number) identified on the blinded portion (Part 3) of the label.

Part 1 of the label should remain on the medication, while Parts 2 and 3 should be removed from the medication and attached to the CRF with transparent tape. Further details and written instructions will be provided by the Site Monitor prior to the study initiation.

B. Dosing Instructions/Schedule

Patients will be instructed to take one capsule from each bottle (bottle A and B) with their morning meal (between 0700 and 0900), and one (from bottle A) with their evening meal (between 1700 and 2000). Patients should take their initial dose on the evening of the day of their baseline clinic visit. At the physician's discretion, patients may be titrated to the maximum dosage (3 capsules/day) by initiating treatment at 1 capsule/day and increasing the dose by 1 capsule every other day. Every effort should be made to sustain treatment at 3 capsules/day. However, patients experiencing adverse experiences may have their dosage reduced; these patients should be titrated upward to the maximum dose as soon as possible.

C. Specifications for Storing, Dispensing, Controlling Inventory, and Disposal of Unused Clinical Trial Material (CTM)

Investigational drug orders, records of CTM receipts, dispensing records, and CTM inventory forms will be examined and reconciled during and at the end of the study. Both the CTM that is used during the course of the study, as well as any remaining unused CTM, must be accounted for on a Drug Disposition Form provided to the Investigator. Unless otherwise directed, at the end of the study all unused and partially used containers of CTM, accompanied by a packing slip, must be shipped to the CTM Management Facility. Instructions for shipment will be provided in the study manual.

In addition, a copy of all completed Drug Disposition Forms must be retained in the Investigator's Study Files. A copy of all completed Drug Disposition Forms must also be sent to the CTM Coordinator at the address indicated for return of the CTM.

The CTM shall be kept in a locked area with limited access under controlled room temperature conditions (15 to 30°C).

V. EXPERIMENTAL PROCEDURES

A. Overview – Schedule of Time/Events (General Specifications)

1. Screening Phase (Week [-8] to Baseline)

During this phase the patient's eligibility for the study will be determined. Several of the assessments made during this period will be used as baseline values.

2. Baseline Phase

Baseline is considered the day on which the first dose (evening) will be given. Baseline assessments will be completed on this day prior to the first dose.

3. Treatment Phase (Weeks 1 to 52)

Outpatients will be dosed *b.i.d.* with the assigned treatment in a double-blind fashion. Clinic visits will occur periodically (see Table 2 on page 10 for schedule) to assess safety and efficacy parameters and to collect plasma samples for pharmacokinetic purposes. Blood samples will be drawn approximately 12 hours after the prior evening's dose and just prior to the morning dose, (before the patient's morning meal, *i.e.*, fasted) during the Treatment Period as indicated in Table 1. All Behavioral and Neuropsychological assessments will take place within 12-24 hours of the last dose of medication. Details of the procedures for obtaining, processing, storing, and shipping of plasma samples are provided in Appendix 2.

4. Placebo Substitution Treatment Phase (Weeks 52 to 104)

Patients will return to the clinic for post-treatment assessments after placebo substitution or continued drug therapy for an additional 52 weeks. In the event patients are discontinued prior to Week 104, the post-treatment assessments will be performed for the last visit after the last dose is taken.

The following table (Table 2) lists the assessments that will be performed during each phase of this study.

Table 2: Study Flow Chart- Baseline Procedures and Group Behavioral and Diet Counseling

Procedure	Week																							
	Treatment													Placebo Substitution Phase										
	BL	1	2	3-12	13	14-18	19-25	26	27-38	39	40-51	52	53-57	58	59-64	65	66-77	78	79-90	91	92-103	104		
Scr	X																							
Entry Criteria	X											X											X	
Physical Exam	X											X						X					X	
Labs	X											X						X					X	
EKG	X											X						X					X	
Urine Drug Screen	X											X						X					X	
Blood for DF & Fluoxetine	X											X						X					X	
Weight/Waist-Hip Circumference	X											X						X					X	
Behavioral and Neuropsychological Testing																								
SCID-I	X											X											X	
SCID-II	X											X											X	
Brown Goodwin Aggression (Life History)	X																							
Wechsler Adult Intelligence-R	X																							
Group Behavior/Diet Counseling																								
Weekly	X	X	X	X	X	X																		
Biweekly						X																		
Monthly											X													
Bimonthly													X	X	X	X	X	X	X	X	X	X	X	X

Table 3: Study Flow Chart- Repeated Behavioral Ratings

Procedure	Scr	BL	Week																
			Treatment							Placebo Substitution Phase									
			8	13	17	26	34	39	43	52	58	65	69	78	86	91	95	104	
Beck Depression		x	x		x		x		x		x		x		x		x		x
Beck Hopelessness		x	x		x		x		x		x		x		x		x		x
POMS		x	x		x		x		x		x		x		x		x		x
Buss-Durkee Hostility Inventory		x			x														
Overt Aggression Scale for Outpatients		x			x														
Barratt Impulsiveness		x			x														
Beck Suicidal Ideation		x	x		x														
Suicide History Short Term		x			x														
Suicide Attempt Lethality Rating		x			x														
Questionnaire on Eating/Weight		x			x														
Stunkard Eating Inventory		x			x														
Rush Sexual Function		x			x														

Table 4: Study Flow Chart - Repeated Neuropsychological Measures

		Week							
		BL	Treatment				52	53-103	104
			1-25	26	27-51	52			
Repeated Tests: Neuropsychological Measures	Scr								
Finger Tapping		x	x				x		x
Choice Reaction Time		x	x				x		x
Continuous Performance Task		x	x				x		x
Stroop ColorWord (computerized)		x	x				x		x
Buschke Selective Reminding Test		x	x				x		x
Verbal Paired Associates		x	x				x		x
Benton Visual Retention: Administration D		x	x				x		x
Visual Paired Faces Associates Tasks		x	x				x		x
Time Estimation		x	x				x		x
Go-No Go Task		x	x				x		x
Logical Reasoning		x	x				x		x
Verbal Fluency		x	x				x		x
Cognitive Failures 25		x	x				x		x

B. Measurements/Evaluations (Detailed Specifications)

SCREENING PHASE

Each of the study sites will randomize up to 160 obese outpatients who satisfy enrollment criteria as detailed below.

Inclusion Criteria

To be considered eligible to participate in this study, the patient must meet the following requirements:

1. Obese patients of either sex who are over the age of 18 and whose obesity is not of endocrine origin, and whose Body Mass Index (kg/m^2) is either $\geq 27 \text{ kg}/\text{m}^2$ with a comorbid condition (e.g., hypertension, diabetes, hyperlipidemia) or $\geq 30 \text{ kg}/\text{m}^2$ with or without comorbid conditions.
2. Women of childbearing potential must have a negative pregnancy test prior to enrollment. Patients of childbearing potential must agree to use a medically accepted form of birth control for the duration of the trial.
3. Prior to screening/baseline evaluations, and following a *full explanation* of the nature and purpose of this study, the patient must consent to participate by signing the Informed Consent document.

Exclusion Criteria

Patients will **not** be eligible for entry into this study if they have any of the following characteristics:

1. Pregnancy or lactation.
2. Hypersensitivity to fluoxetine, dexfenfluramine, d,l-fenfluramine, or chemically related agents.
3. Diagnosed pulmonary hypertension.
4. Endocrine causes of obesity.
5. Illicit drug use within the past six months or confirmed positive findings of illicit drugs in a urine drug screen (e.g., amphetamines, cocaine, hallucinogens, THC).

6. Treatment with any investigational new drug in the past 60 days.
7. Individuals who require treatment with a serotonergic agent or a monoamine oxidase inhibitor (see also the list of disallowed concomitant medications in Table 6).
8. Individuals taking anorectic drugs (*e.g.*, phentermine).
9. Patients who have taken either fluoxetine, fenfluramine (Pondimin®) or dexfenfluramine (Redux™) for more than 1 month in the past year.
10. History or presence of narrow angle glaucoma.
11. Patients who express an intention to relocate out-of-town during the study period (*i.e.*, 2 years).
12. Patients with any characteristic that would preclude their taking one of the neuropsychological testing procedures (*e.g.*, color blindness, amputation, dementia, IQ <80 on WAIS-R).

Patients will be advised that side effects of the medications could affect their ability to engage in potentially hazardous activities, such as operating heavy machinery. Their ability to drive may also be adversely affected.

Patients will be screened initially to determine if they meet readily discernible enrollment criteria (*i.e.*, those criteria *not* requiring laboratory evaluation or special studies). Those patients who meet these requisites will undergo additional assessments including blood chemistry, hematology, urinalysis, neurologic examination, and assessment of baseline screening phase signs and symptoms.

BASELINE PHASE

Patients who meet all of the inclusion (and none of the exclusion) criteria will be assigned to a treatment group (Table 5) according to the randomization code, (see *Study Design*), and provided with a 5-week supply of study medication. Each patient will be instructed to ingest the *first* dose during the evening meal on the day the medication is dispensed. Patients will be instructed to call their physician before taking another dose if any unusual effects are observed following the initial dose.

Otherwise, the patient will commence a *b.i.d.* regimen the following day or, alternatively, increase the dose by one capsule every other day at the physician's discretion. All patients should be at the maximum dose (3 capsules/day) by the end of week 1.

Table 5. Treatment Groups

GROUP	TREATMENT Total Daily Dose	TREATMENT REGIMEN (<i>b.i.d.</i>)	
		Morning Meal (2 capsules ^a)	Evening Meal (1 capsule ^b)
I	Dexfenfluramine, 30 mg	15 mg	15 mg
II	Fluoxetine, 60 mg	40 mg	20 mg
III	Placebo	P	P

^a 1 capsule from Bottle A and 1 capsule from Bottle B

^b 1 capsule from Bottle A

In addition to receiving study medication, patients will be instructed to adhere to a calorically-restricted diet. As described under Treatment Phase, this diet will be gender- and body weight-specific. Also, all patients will be given exercise instruction (and encouragement) and group behavior modification sessions.

- **PHYSICAL EXAMINATION**

- **BEHAVIORAL AND COGNITIVE TESTS**

Patients will receive a set of baseline measures that will be repeated only at the major endpoints of the study (see Tables 2-4). Other measures in specific Behavioral and Neuropsychological Domains will be administered at baseline, and periodically over the 2 year study duration as shown in Tables 2-4. The Neuropsychological Tests that are sensitive to content-related practice effects will have three alternate forms. These forms will be randomized across patients, and then alternated in a fixed order within patients. In this way, each patient will receive the same version of the test at baseline, 12 months, and 24 months.

- **VITAL SIGNS (Sitting Blood Pressure, Peripheral Pulse)**

- **LABORATORY TESTS (Appendix 4)**

- **ADVERSE EVENTS (Baseline Signs and Symptoms)**
- **CONCOMITANT MEDICATIONS**
- **MEDICAL EVALUATIONS**
- **WEIGHT**

TREATMENT PHASE

The effectiveness of the various treatments as an adjunct to reduced caloric intake will be assessed by percent change (from baseline) in body weight. Patients will be weighed and measured in indoor clothing without shoes at each clinic visit. An appetite questionnaire will be administered at the times indicated in Table 2.

Blood samples will be drawn approximately 12 hours after the prior evening's dose and just prior to the morning dose, (before the patient's morning meal, *i.e.*, fasted) during the Treatment Period as indicated in Table 2. Details of the procedures for obtaining, processing, storing, and shipping of plasma samples are provided in Appendix 2.

Patient compliance with the dosing regimen will be assessed by pill counts and drug accountability records.

The safety of the various treatments will be assessed as follows:

- **PHYSICAL EXAMINATIONS**
- **BEHAVIORAL AND COGNITIVE TESTS (Tables 2-4)**
- **GROUP BEHAVIOR MODIFICATION AND DIET INSTRUCTION**

Patients in all three treatment conditions will receive a program of behavior modification, designed to improve eating and exercise habits, as well as to facilitate medication adherence. Treatment will be delivered to groups of 8-12 participants in weekly or every-other-week meetings of 75 minutes duration. This program has been shown to induce an average loss of approximately 5% to 8% of initial weight when used without medication, and a loss as great as 15% of initial weight when used in combination with fenfluramine or the fenfluramine-phentermine combination. We believe that the provision of group behavior modification will improve subject retention in the study, particularly that of persons assigned to the placebo condition. Approximately 85% of persons remain in behavioral treatment after 6 months and 75% after 1 year. Patients in the proposed study will attend a total of 32 group treatment sessions during the first 52 weeks and 6 sessions from weeks 53-104.

Weeks 1-18. During the first 18 weeks, patients will attend weekly group sessions, which will be conducted using the LEARN Program for Weight Control, a copy of which will be given to patients. Patients will be told that combining medication with the modification of eating, exercise, and thinking habits will result in optimal changes in weight and health. Participants will complete weekly assignments which will be reviewed and collected at treatment meetings. This will include keeping weekly records (for a minimum of the first 18 weeks) of their food intake, physical activity, and medication adherence. Patients will be weighed at all treatment visits.

Women will be instructed to consume a low-fat, balanced diet of approximately 1200 kcal/d and men, a diet of approximately 1500 kcal/d, as described in the LEARN manual. In both cases, patients will be instructed to consume a diet of their choosing but to decrease their consumption of fat and sugar. Persons who report difficulty in selecting a healthy diet will be provided sample menus. Activity goals will include eventually walking 4 to 5 times weekly for 30 to 40 minutes at a time, and expending an extra 50-100 kcal/d in lifestyle activity. Patients will be provided additional instruction (beyond that contained in the LEARN manual) on methods of setting realistic expectations for changing weight, health, and appearance. Methods of developing and adhering to a medication schedule also will be covered.

Weeks 20-40. During weeks 20-40, patients will attend group sessions every-other-week (a total 11 meetings) and complete readings and assignments in the Weight Maintenance Survival Guide. These meetings will cover the skills required for the maintenance of weight loss which include: 1) exercising regularly; 2) identifying high risk situations for dietary lapses; and 3) developing social support.

Weeks 41-52. During weeks 41-52, patients will attend monthly group meetings (at weeks 44, 48, and 52) at which their progress will be reviewed. Staff will help patients trouble-shoot any difficulties they report. Participants will be asked at each meeting to set behavioral goals for the next session.

Weeks 53-104. Patients will attend 6 every-other-month sessions during the second year. Participants will review their progress in adhering to healthy eating and exercise habits and in maintaining their weight losses. Patients will set behavioral goals at each sessions to be completed before the next meeting.

- VITAL SIGNS (sitting blood pressure, peripheral pulse.)
- LABORATORY TESTS (Appendix 4)
- ADVERSE EVENTS (spontaneously reported or elicited by a non-suggestive probe)
- CONCOMITANT MEDICATION RECORDS
- MEDICAL EVALUATIONS

The schedule for these assessments is given in Table 2. Data obtained from the various types of patient evaluation will be subjected to appropriate statistical analysis (see *Statistical Analysis* for specific methods).

OVERDOSE

In the event of patient overdose, general supportive measures for oral drug overdose should be instituted. This may include aspiration of gastric contents, gastric lavage with activated charcoal, and careful monitoring for Central Nervous System (CNS) or respiratory depression. Other measures that have been taken include forced diuresis to accelerate urinary elimination of the drug. Patients should be closely followed until there is no further evidence of drug-related CNS effects. No specific antidote is available for dexfenfluramine or fluoxetine.

POST-TREATMENT PHASE

Following the last dosing (on the morning of the Month 24 visit), patients will be instructed to complete all of the post-treatment follow-up assessments. The assessments to be performed are listed in Table 2-4.

If any clinically significant abnormalities not present at baseline are detected during the course of the post-treatment evaluations, then the patient will be monitored until the parameter in question returns to baseline level, or until the parameter is no longer judged to be clinically significant by the Investigator and the Medical Monitor.

In addition, immediately following the conclusion of the Month 24 clinic visit, (or if a patient discontinues, prior to this), a CRF Termination Page will be completed. Also, any termination more than one month following a scheduled assessment will require a complete termination behavioral and neuropsychological assessment.

VI. PROCEDURES FOR ADVERSE EXPERIENCES

A. Adverse Experience Reporting

The date and time of onset, duration, treatment, and outcome of each adverse experience must be recorded on the appropriate CRF. In addition, the investigator must provide a judgement of the severity of each event and its relationship to the study treatment. Each alarming adverse event must be followed by the investigator until it is either resolved or determined to be a stable or chronic condition.

B. Special Reporting Procedure for Death, Alarming, or Serious Adverse Experiences

In the event of a death, alarming, or serious adverse experience, the study monitor or medical monitor must be contacted immediately by telephone. In the event that the monitor cannot be reached, a message must be left at the emergency number noted in the study manual within 24 hours of the incident.

An alarming adverse experience is any experience that, in the judgement of the investigator, causes concern for the patient's safety. This also includes any experience that, in the judgement of the investigator, is unusual or unexpected.

A serious adverse experience is any experience that suggests a significant hazard, contraindication, side effect, or precaution. With respect to human clinical experience, a serious adverse drug experience includes any experience that is fatal or life-threatening, is permanently disabling, requires or prolongs hospitalization, or is a congenital anomaly, cancer, or the result of an overdose.

The adverse experience must be completely described on the patient's CRF.

Any adverse experience that is determined by the sponsor to be reportable to the FDA as an IND Safety Report should be promptly reported to the Institutional Review Board (IRB). The investigator will promptly supply all information identified and requested by the sponsor or Medical Monitor regarding the adverse experience.

The investigator must promptly report to the IRB all unanticipated problems and adverse experiences involving risk to human patients.

VII. TERMINATION OF A CLINICAL STUDY OR PATIENT DISCONTINUATION

A. Termination of a Clinical Study

If Interneuron Pharmaceuticals, Inc. or the Principal Investigator discovers conditions arising during the study which indicate that the clinical investigation should be halted, the study must be terminated after appropriate consultation between the Interneuron Pharmaceuticals, Inc. and Principal Investigator. Conditions that may warrant termination include, but are not limited to:

- The discovery of an unexpected, significant, or unacceptable risk to the patients enrolled in the study,
- Failure of the Investigator to enter patients at an acceptable rate,
- Insufficient adherence to protocol requirements.

B. Patient Discontinuation

If a patient is discontinued from the study prematurely, the Investigator will provide a written report on the appropriate CRF page describing the reason for discontinuation. As noted above, any termination more than one month after a scheduled assessment will require complete termination behavioral and neuropsychological assessments to be performed. These will be carried forward in an intent-to-treat analysis.

A patient may be removed from the study for the following medical or administrative reasons:

Adverse Experience: If a patient suffers an Adverse Experience that in the judgment of the Principal Investigator, Interneuron Pharmaceuticals, Inc., or the Medical Monitor presents an unacceptable consequence or risk to the patient, the patient may be discontinued from further participation in the study.

Intercurrent Illness: If a patient develops an illness during the course of the study that is not associated with the condition under study, and which requires treatment that is not consistent with protocol requirements, the patient may be discontinued from further participation in the study. A patient may also be discontinued from the study if, in the judgment of the Investigator, the patient develops an intercurrent illness that in any way justifies his or her withdrawal.

Administrative Discontinuation: After consultation with Interneuron Pharmaceuticals, Inc. or the Medical Monitor, a patient may be discontinued from the study for the following administrative reasons: (1) failure to visit the clinic at the scheduled dates, (2) unauthorized, patient-initiated changes in dosing regimen or dose, (3) failure to comply with protocol requirements, or (4) failure to take study medication. All instances of noncompliance must be documented in the CRF.

Refusal of Treatment: If for any reason the patient refuses treatment during the study, the patient shall be discontinued from the study and the reasons for refusal documented on the CRF. Reasonable efforts shall be made to monitor the patient for Adverse Experiences following such discontinuation. Such efforts shall be documented on the CRF.

VIII. CLINICAL DATA COLLECTION AND PROCESSING/STATISTICAL APPLICATION - DATA ANALYSIS

A. Clinical Data Collection and Processing

Case Report Forms will be provided to the study site by the Sponsor. The data collected during the study should be typed or printed onto the CRF using a **ballpoint pen with black ink or typed using black ink**. All deletions or corrections to the CRF should be initialed and dated. Opaque correction fluids are not permitted.

B. Statistical Analysis

After review by the Site Monitor, the completed CRF will be forwarded to the data collection center. Instances of missing or uninterpretable data will be discussed with the Investigator for resolution. The data will be entered into a computerized database and a quality assurance audit will be performed on the database. The analyses to be conducted are described below:

1. Interim Analyses

Two interim analyses of the behavioral and neuropsychological data will be performed when approximately 160 and then 320 patients have completed the 6 month assessments (Tables 2-4). The value for all comparisons will be maintained at $p \leq 0.05$ (*i.e.*, no adjustment for the interim analysis) as this is the most conservative approach, given the objectives of this study.

2. Data Sets

Unless otherwise specified, the main analyses will employ the Intent-to-Treat (ITT) sample, Last Observation Carried Forward (LOCF) data set; confirmatory analyses will be conducted on the observed cases (OC) at each time point and completer data sets to examine the effect of patient discontinuation on the findings.

3. Behavioral and Neuropsychological Tests

The analyses presented below aim to maximize detection of the potential adverse effects of dexfenfluramine in any of the behavioral and neuropsychological measures (at the risk of inflating Type 1 error rates). In particular, we will conduct both univariate and multivariate analyses of these measures. This strategy reflects the fact that the protocol is a Phase IV post-marketing study rather than a Phase III efficacy study. We will conduct analyses especially designed to identify patients with marked abnormalities and to detect subtle, cumulative adverse effects in each treatment group, if any.

a. Descriptive Analyses

We will conduct a series of descriptive, non-parametric analyses to inspect the data, investigate the distributions of the raw scores, and identify outliers that may potentially invalidate the parametric analyses described below. Particular emphasis will be given to providing means and mean placebo-dexfenfluramine and placebo-fluoxetine differences with 95 percent confidence intervals for each outcome measure.

b. Univariate Analyses

For each of the outcome measures (raw scores), we will conduct three types of analyses:

- i Analysis of covariance using all patients (based on the "intent-to-treat, LOCF" principle), where, for patients who did not complete the one-year follow-up, the six-month score (or the last recorded observation) is substituted for the missing one-year score. Treatment group assignment will be a between-patients term and the raw scores for the dependent measures will be used.
- ii Random regression analysis (which is a generalized version of the repeated measures ANOVA techniques) where all the data available on all patients will be used. This technique allows the estimation the effect of treatment, adjusting for the effect of time-dependent covariates. The use of all observations on all patients in the random regression analyses will allow for interpretation of the effects of subject dropout on the results of the ANCOVAs. The use of time-varying covariates in the random regression analyses will allow for examination of the contribution of potential moderating or suppressor variables to the pattern of between-group differences, e.g., differential weight loss or mood change.

For the analyses of covariance, we will test the critical assumption of equality of slopes among the three groups. A liberal threshold will be used to detect violation of homogeneity (i.e, $p < 0.15$). Examination of this assumption for the neuropsychological measures will permit an investigation of a potential differential "practice effect" in the three groups. Any group differences in the magnitude of practice effects will be further investigated and substantively interpreted. Diminished practice effects in a particular treatment condition would indicate neuropsychological impairment.

As indicated, comparisons of the results of the three types of analyses will provide valuable information about the potential biases due to drop-outs. However, we expect that the results across the three types of analyses will be consistent.

In all parametric analyses, we will use the placebo group as a "reference" group, so that estimates (and standard errors) of the differential effect of the two active drugs vs. placebo will be obtained directly from these analyses. Consequently, in the context of significant main effects or interactions involving treatment group, post-hoc comparisons will first examine potential differences between the dexfenfluramine group and the placebo or fluoxetine groups, without correction for multiple comparisons.

iii. Multivariate Analyses

For the behavioral and neuropsychological measures grouped by conceptual domain, we will also conduct ten separate MANCOVA analyses. These MANCOVAs will be conducted on the raw scores for the dependent variables within a domain, using the baseline scores as covariates (with four domains for the behavioral measures and six domains for the neuropsychological measures). These analyses will permit the investigation of overall treatment effects in each domain (e.g., the collection of a significant overall effect on the "depression" or "attention/concentration" domain. The univariate analyses conducted in Step 2 will provide detailed information about the contribution of each measure in the domain to this overall effect. Again, we will focus primarily on the estimation of differences between the dexfenfluramine group and the placebo or fluoxetine groups, without correction for multiple comparisons.

4. Analysis of "Rare Events"

We will carry out two types of analyses to investigate the presence of marked or subtle deficits that might not be reflected in group means.

a) Analysis of Variance on Impairment Scores

We will construct a quantitative "Impairment Score" equal to the number of times a subject falls more than 0.5 SD below the mean change score on the dependent measures. Separate "total" impairment scores will be computed for the behavioral and neuropsychological measures. ANOVA of these quantitative total impairment scores will permit the detection of consistent patterns of impairment for patients in any of the three treatment groups.

b) Logistic Regression Modeling of the Frequency of Patients Exceeding Cut Off

These analyses will be conducted separately for each dependent measure. We will count the number of patients who fall more than 0.5 SD below the mean change score in each treatment group and at each time point. These counts will be used as the dependent variable in logistic regression models to investigate the effect of treatment, time, and treatment-by-time interactions. Results of these analyses will provide information about the existence of main treatment effects, time trends, and possible differential patterns of treatment effects over time.

If any of these analyses show significant results, we will examine the subgroup of patients for whom these deficits exist and attempt to characterize these patients based on clinical and/or demographic variables. Note that these *a posteriori* analyses (namely, the identification of the variables that distinguish patients particularly at risk for adverse effects) will be exploratory in nature and would need confirmation. We will use re-sampling techniques (e.g., bootstrap methods) for a non-parametric assessment of the statistical significance of the putative predictors of patients at higher risk for adverse effects.

5. Effect of Moderator Variables

a) Gender Effect

The design calls for stratifying the randomization by gender, thus minimizing the possibility of biases due an imbalance in numbers of males and females in the treatment groups and/or an imbalance in the distribution of important (but unknown) covariates associated with outcome. We will study whether there are gender

differences by using gender as a between-subject covariate in the parametric analyses.

b) Weight Loss

It is expected that the magnitude of persistent weight loss will differ among the groups. Potentially, this difference could exaggerate or suppress treatment group differences in some behavioral or neuropsychological measures. To examine this possibility, the random regression analyses (Step 2) will be repeated using the amount of weight loss (percentage of initial weight) as a time-varying covariate. In addition, the sample will be subsetted, and the analyses conducted in Step 2 repeated separately for the groups with and without substantial weight loss.

c) Other Moderator Variables

Other moderator variables, *e.g.* blood lipid levels, will be examined as described for weight loss.

6. Safety Analysis

Safety analyses will include all patient data.

a. Safety Assessments to be Examined:

- Physical and Neurological Examinations
- Adverse Events
- Vital Signs

b. Statistical Methodology for Safety Analysis

Adverse events, if any, will be tabulated and between-treatment comparisons made using Chi-Square tests for homogeneity of proportions or appropriate exact test methodology. Adverse events will be classified according to a COSTART dictionary.

Treatment comparisons will be performed for overall incidence for at least one event and within body system. Patients will be counted more than once if adverse events occur in multiple body systems, but only once within a body system for purposes of statistical analyses.

7. Other Analyses

Compliance with prescription of study medication will be assessed from pill counts, drug accountability records, and from plasma concentration measurements.

8. Pharmacokinetics

Trough plasma concentrations will be examined for evidence of accumulation of dexfenfluramine or fluoxetine. Descriptive statistics such as means, standard deviations, minimum values, and maximum values will be presented by timepoint and for the entire study duration. Confidence intervals for pharmacokinetic data will be included in all presentations. The relationship between pharmacokinetic data will be compared to selected efficacy variables using parametric and non-parametric techniques.

C. Statistical Power Considerations for Behavioral and Neuropsychological Tests

The hypothesis, based on biochemical studies in animals, is that dexfenfluramine will have a consistent effect on serotonergic neuronal function that varies in intensity as a function of exposure. Therefore a measure of mean changes is most appropriate.

The ANCOVA of each behavioral or neuropsychological domain on the intent-to-treat sample, last observation carried forward data set was considered the primary analysis for estimating power. Due to the wide range of raw score values, power analyses were expressed in standardized units calculated by dividing the difference between the observed value and the mean baseline value by the standard deviation for that test in this study (i.e. Z scores; mean = 0, SD = 1) so that the power estimates are comparable across all domains. Test/retest correlations of 0.4 for the behavior tests and 0.7 for the neuropsychological test were selected based on historical data. Significance would be declared at $p \leq 0.05$ with no adjustment for multiple comparisons.

Based on the above considerations a sample size of 160 patients per treatment in Phase 1 of the study has a power of $\geq 85\%$ to detect an effect size of 0.3 SD on any behavioral or neuropsychological domain. An effect size of 0.3 SD is a difference of at least 50% that observed between normal patients and mildly ill psychiatric outpatients on the outcome scales selected. For example, in a previous study involving 335 non-depressed, obese outpatients the mean HAM-D score at baseline

was 3.7 ± 2.9 (SD). Thus this study is powered to detect a change in group mean HAM-D score of 0.9; a change in group mean HAM-D scores of 3 is generally viewed as clinically significant.

Based on a 70% entry rate into Phase 2 from Phase 1, the power for Phase 2 is $\geq 80\%$ for an effect size of 0.4SD based on a total of 5 treatment groups.

The sample size for the placebo and dexfenfluramine groups was set at 240 at the request of FDA (June 26, 1997). The sample size for the fluoxetine group was set at 160 based on the power calculation described above.

IX. CLINICAL STUDY ADMINISTRATION (also see Appendix 3)

A. Informed Consent

Signed Informed Consent must be obtained from each patient prior to commencing Screening/Baseline evaluations. One copy of the signed Informed Consent document will be given to the patient and another retained by the Investigator.

The Informed Consent document must have been reviewed and approved by the Sponsor and the Investigator's IRB prior to initiation of the study.

A prototype Informed Consent for this study is located in Appendix 1; this document contains all required elements, viz.:

1. Required Elements

- a. A statement that the study involves research; the purpose of research; the expected duration of patient's participation; and a description of procedures.
- b. A description of reasonably foreseeable risks or discomforts to the patient.
- c. A description of any benefits to the patient or others which may be expected from the research.
- d. A disclosure of appropriate alternative procedures or courses of treatment.
- e. A statement regarding the extent to which the confidentiality of records will be maintained. Note: FDA may inspect all records.

- f. A statement regarding compensation/medical treatment for injury.
- g. An explanation of whom to contact for answers to pertinent questions about the research or in the event of research-related injury.
- h. A statement that participation is voluntary, refusal to participate will involve no penalty or loss of benefits to which the patient is otherwise entitled, and that the patient may discontinue participation at any time without penalty or loss of benefits.

2. Optional Elements

- a. A statement that particular treatment or procedure may involve risks to the patient which are currently unforeseeable.
- b. A description of the circumstances under which the patient's participation may be terminated by the Investigator without regard to the patient's consent.
- c. A description of additional costs to the patient that may result from participation.
- d. A description of the consequences of a patient's decision to withdraw from the study and the procedures for termination of participation by the patient.
- e. A statement that significant new findings developed during the course of the research which may relate to the patient's willingness to continue participation will be provided to the patient.
- f. A description of the approximate number of patients in the study.

B. Study Documentation

Study medication will be provided to the Investigator after he has submitted the following documents:

- a. Signed protocol,
- b. Signed Statement of Investigator (Form FDA 1572),
- c. Document indicating IRB approval of the final protocol and Informed Consent document (to include name, address, and chairperson of the IRB),

- d. IRB member list
- e. Signed Investigator's Agreement and Letter of Confidentiality,
- f. Curricula Vitae for: the Investigator; and
the Sub-Investigator(s).

Copies of the foregoing, as well as supplemental information such as the Investigator's Brochure and Investigator/Study Monitor/Sponsor Responsibilities and Obligations (see Appendix 3), should be kept on-site in a special study file. This file should also contain drug accountability (receipt/dispensing) records, Sponsor/Study Monitor/Investigator correspondence, monitoring reports, patient exclusion records, and CRFs.

2. Case Report Forms (CRFs) and Source Documentation

All required study information must be recorded (with a ball-point pen with black ink) on the CRFs provided. In addition, the Investigator must sign each patient's CRF to signify that the information is correct and complete. In the event of an error, a *single* line should be drawn through the incorrect information and the correction recorded. Opaque correction fluid is not permitted. (NOTE: This change must be initialed and dated by the Investigator or his/her designee).

The original CRFs for each patient will be checked against source documents at the study site by the Site Monitor. A copy of the final CRF will be placed in the Investigator's study file and the original will be taken by the Site Monitor to the data center.

3. Retention of Study Documents

All CRFs, as well as supporting documentation and administrative records, by law must be retained by the Investigator for *a minimum of two years following notification* that the study is discontinued. No study documents should be destroyed or moved to a new location without prior written approval by Interneuron Pharmaceuticals, Inc.

C. Confidentiality

All study findings and documents will be regarded as confidential. The Investigator and members of his/her research team must not disclose such information without prior written approval from Interneuron Pharmaceuticals, Inc.

The anonymity of participating patients must be maintained. Patients will be identified on CRFs and other documents by their initials, birth date, and patient number. Documents not to be submitted which identify the patient (e.g., the signed Informed Consent), must be maintained in strict confidence by the Investigator.

D. Departure from Protocol

Should a departure from protocol be deemed crucial for the safety and well-being of a particular patient, such a departure will be instituted for that patient only. The Investigator or other attending physician should contact the Medical Monitor as soon as possible (see *Reporting of Adverse Events*). In addition, the Investigator should document in the patient's CRF the reasons for protocol deviation and the ensuing events.

Substantive changes in the protocol must be prepared by Interneuron Pharmaceuticals, Inc. and must receive IRB approval prior to implementation. The protocol amendment will be submitted to the IND under which the study is being conducted.

E. Monitoring Functions/Responsibilities

The progress of the study will be monitored by:

1. Periodic on-site reviews,
2. Frequent telephone communications between the Investigator and Study Monitors, and
3. Review of CRFs and clinical records.

Representatives of Interneuron Pharmaceuticals, Inc. may accompany the Site Monitor to the site.

F. General Information for Investigators

Investigators are referred to the associated Investigator's Brochure, approved product labeling, information provided by the Site Monitor, the study manual, or the appendices of this clinical study protocol for further information regarding the details of the procedures to be followed during the course of this study.

APPENDIX 1

CONSENT TO PARTICIPATE IN A CLINICAL RESEARCH STUDY

STUDY TITLE: The Effects of 12 and 24 Months of Dexfenfluramine Treatment on Neuropsychological Function in Obese Patients.

PROTOCOL NUMBER: IP96-007

SPONSOR: Interneuron Pharmaceuticals, Inc., Lexington, MA.

GENERAL STATEMENT AND BACKGROUND

I have been asked to participate in a research study of a drug for controlling obesity, called dexfenfluramine hydrochloride (tradename: Redux™). Dexfenfluramine helps to reduce hunger, caloric intake, and body weight gain in humans and animals. This drug is thought to help patients reduce their food consumption, specifically the consumption of carbohydrates. Dexfenfluramine is associated with changes in neurotransmitter (chemical) systems in the brain and may affect the patient's feeling of fullness. At doses of about 30 times that used clinically, the amount of a neurotransmitter called serotonin that is present in the brains of animals is reduced with dexfenfluramine treatment.

Fluoxetine (Prozac®), a drug used to treat depression, is being used in this study for comparison to dexfenfluramine because it also affects the neurotransmitter serotonin. While fluoxetine has been used in clinical studies to reduce body weight, it is not approved for the treatment of obesity.

Placebo (inactive study medication) is also being used in this study for comparison with the dexfenfluramine and fluoxetine treatments.

PURPOSE

The purpose of this study is to determine the effect of two different medications, dexfenfluramine (Redux™) and fluoxetine (Prozac®) on my mood, appetite and my ability to perform cognitive (thinking or reasoning) tests. During the study, I will follow a strict diet, which is prescribed for me. This study will also look at any side effects that might occur from withdrawal of the drug after the end of treatment and observe how body weight responds months after treatment is over. This study will compare all these results to those observed with placebo.

BENEFITS

I understand that the advantage of being in this study is that I may lose weight, the amount of which will vary by individual. Additionally, I will receive very close attention by the study staff during the time I am involved in the study. However, I understand that I may not benefit from this study and that no guarantees have been made to me.

ALTERNATIVES

I understand that there are other methods available to me for treating my obesity. Decreased food intake, increased exercise, and behavioral modification therapy, or a combination of these, may help me to lose weight. Other anti-obesity treatments can also be used to treat my obesity.

RISKS

All weight loss treatments may have adverse effects. A serious adverse effect reported with the use of appetite suppressants, including dexfenfluramine, is primary pulmonary hypertension (raised blood pressure within the blood vessels supplying the lungs). Non-serious adverse events which may be associated with dexfenfluramine include gastrointestinal upset, malaise (a feeling of illness or discomfort), headache, and changes in mood. Dexfenfluramine may also impair concentration or cause sedation. The most frequent adverse events associated with dexfenfluramine treatment were as follows: gastrointestinal complaints, including diarrhea and dry mouth; nonspecific systemic effects, including fatigue and tiredness; nervous system symptoms, including headaches, anxiety, depression, dizziness, drowsiness, decreased concentration, and polyuria (excretion of an excessive amount of urine).

In animals receiving high doses of dexfenfluramine for short periods of time that resulted in brain concentrations approximately 10 times those seen in humans, changes in a brain chemical (serotonin) were observed. These changes were generally reversed over time but persisted over a year in one study of three animals. The importance of these findings to humans is not known.

Non-serious adverse events that may be associated with fluoxetine treatment include nervous system complaints including anxiety, nervousness, insomnia; drowsiness and fatigue or asthenia; tremor; sweating; gastrointestinal complaints, including loss of appetite, nausea, and diarrhea; and dizziness or lightheadness.

As with all research studies, the drug treatment and study procedures in this investigation may involve unknown risks. One of the unknown risks being investigated in this study is the effect of neurotransmitter changes during long term treatment with these types of drugs.

I understand that all medications can have side effects, including adverse reactions. I also understand that my symptoms may not be controlled by the treatments used in this study.

Blood samples will be drawn on scheduled visits (during the screening examination and at baseline and five of the monthly visits over 24 months). Some known risks, although rare, that can be associated with the blood drawing procedure are pain, burning, or the development of a bruise or infection at the site where the needle is placed to draw the blood.

STUDY DESCRIPTION

The maximum length of time of my participation in this study is 24 months. I will be one of approximately 640 patients participating in this study at several locations throughout the country. The first two weeks of the study will involve initial evaluations (called screening evaluations). If I am found eligible for the study during these two weeks, I will be randomly assigned to one of three groups and will receive either placebo (inactive study medication), dexfenfluramine (30 mg/day), or fluoxetine (60 mg/day) for up to 24 months. I will take three capsules of medication every day by mouth, two capsules with my morning meal and one capsule with my evening meal. I understand that whether I take dexfenfluramine, fluoxetine or placebo is decided randomly (that, is, by chance), and that neither I nor my doctor will know which treatment I am taking. I may be assigned to one treatment for part of the study and another for another part of the study.

While participating in this study, I must return for scheduled visits and treatment. Prior to and during the study, I understand that I must have the following procedures done at no cost to me: physical exam, blood and urine lab tests, body measurements and behavioral and cognitive (thinking) tests. I will fill out a questionnaire during each visit about my food preferences and appetite, and will report all changes in my mental and physical condition during the course of the study whether or not I feel they are related to the study. I will be monitored throughout the study for adverse events, intercurrent illnesses, and medications taken at the same time as the study treatment, and for dosing compliance. I will also receive diet and exercise counseling from baseline (immediately before first dose of medication) through Month 24 of the study.

I understand that I will be encouraged to increase my amount of physical activity throughout the study.

I am aware that I need to assess the effects of the study medication on me before engaging in potentially hazardous activities, such as driving a motor vehicle or operating heavy machinery, while I am enrolled in this study.

I understand that I must have a negative pregnancy test prior to enrollment, if I am a woman of childbearing potential. If I am at risk of becoming pregnant, I must use a medically accepted form of birth control throughout the study. Additionally, I must not be nursing an infant during the study.

PATIENT RIGHTS

I am aware that in the event of injury resulting from participation in this research study, any medical treatment which is necessary will be provided to assist my recovery from the injury. There will be no charge for this care beyond what is covered by my health insurance. This agreement to provide free medical treatment does not include treatment for any illness I might experience during the course of this study if the illness is not the result of participation in the research study. No compensation other than free medical treatment of this injury will be provided. If I experience an adverse reaction or injury, and if emergency medical treatment is required, I will report immediately to: _____.

I understand that participation in this study is voluntary and that my refusal to participate will involve no penalty or loss of benefits to which I am otherwise entitled. If I decide to participate, I may change my mind about being in the study, and I may stop at any time without penalty or loss of benefits regarding my future care. Significant new findings which may develop during the course of the research study which may affect my willingness to continue participating in this study will be brought to my attention by the doctor conducting this study.

I understand that my doctor has the right to withdraw me from the study at any time he/she feels that is in my best interest. I also understand that if I withdraw voluntarily or am withdrawn by my doctor, I may be asked to cooperate in having whatever laboratory tests and examinations my doctor thinks necessary.

Absolute confidentiality cannot be guaranteed; however, I understand that all medical records and research materials which would identify me will be held confidential. I hereby grant permission for medical information about me obtained during this study to be made available to authorized representatives of the Food and Drug Administration, and other government agencies and to representatives of Interneuron Pharmaceuticals, Inc. or their agents, and to other physicians, nurses, or study personnel who may be evaluating this medication. I understand that if the results of this study are published in the medical literature, I will not be identified by name.

I have fully discussed and understand the purpose and procedures of this study which have been explained to me by the undersigned. I have been invited to ask any questions that I have about the study, and all my inquiries have been answered. The following are the names, and telephone numbers of persons who are not associated with this research to whom I may address complaints about this study, as well as questions about the research and my rights as a research participant: _____ Phone: () _____.

All oral and written information and discussions about this study are in English, a language in which I am fluent.

I acknowledge that I have been given a copy of this consent form.

Having thoroughly read, understood, and had a full explanation of the above information, I voluntarily consent to participate in this study. If I have any additional questions later, I understand that I can contact _____, at telephone () _____.

Signature of Patient

Date

Printed Name of Patient

Signature of Witness

Date

INVESTIGATOR STATEMENT

I, the undersigned, certify that to the best of my knowledge the patient signing this consent had the study fully and carefully explained and clearly understands the nature, risks, and benefits in his/her participation in this research study.

Signature of Principal or Co-Investigator

Date

IRB Approval Date: _____

APPENDIX 2

PROCEDURES FOR OBTAINING, PROCESSING, STORING, AND SHIPPING OF PLASMA SAMPLES

All samples must be labeled with the information identifying the patient and sampling time. The storage time and temperature must also be recorded.

PLASMA SAMPLES

Venous blood samples will be drawn from an antecubital vein into a 10-ml heparinized green-top tube for determination of plasma concentrations of fluoxetine and its metabolite, norfluoxetine, dexfenfluramine and its metabolite, d-norfenfluramine. Blood samples should be immediately placed in a refrigerated environment (approximately 4°C) and centrifuged no later than 20 minutes after the blood draw at 3,000 x g for 15 minutes. The resulting plasma should be transferred approximately equally to two polypropylene screw cap vials (5-ml capacity) and stored at -20°C. One vial of each sample should be designated as the primary sample. This will be the vial to be shipped for analysis as described below. The second vial should remain at the site (stored at -20°C) as a backup until the final study medical report has been completed.

Plasma samples obtained during the Treatment Phase will be shipped from the study site on a monthly basis for analysis. When plasma samples are ready to be shipped, store on dry ice in an insulated carton and send immediately by Overnight Express Mail to the address noted in the study manual.

Samples must be placed for shipping in sufficient dry ice to maintain them in a frozen state for at least 72 hours. A small temperature detector (provided to the Investigator by the Site Monitor) will be placed in the center of the shipping carton. At the time of the shipment, the laboratory personnel should be notified by FAX at the number noted in the study manual.

All shipments must be made no later than Wednesday in order to assure delivery by Friday of the same week. Include in the shipment a shipping manifest summarizing each specimen being shipped, (including patient's initials, patient's study identification number, sample identification, and sampling date and time). The Site Monitor will provide the Investigator with blank forms onto which this information should be recorded.

APPENDIX 3

**SPONSOR/STUDY MONITOR/INVESTIGATOR
RESPONSIBILITIES AND OBLIGATIONS**

Sponsor/Study Monitor

The sponsor, or his/her designated representative, the Monitor, will:

A. Conduct a pre-investigation visit to:

1. Establish the acceptability of the facility and record this in a written report (memorandum or form).
2. Discuss the proposed clinical trial with the Investigator, supply him/her with the Investigator's Brochure, and the protocol for his/her review and approval.
3. Discuss with the Investigator FDA requirements with respect to Informed Consent, IRB approval of the trial, the protocol, and protocol amendments and changes to the Informed Consent.
4. Discuss with the Investigator the timing of interim and final reports to the Monitor, and his/her obligation to supply the Monitor with copies of all trial-related documents (IRB approval, IRB charter or equivalent, membership and qualifications, protocol amendments, Informed Consent, consent changes, case record, case record changes, and all pertinent correspondence to and from the IRB).

B. Conduct periodic on-site visits to:

1. Assure adherence to the protocol.
2. Review CRFs and patient medical records for accuracy and completeness of information.
3. Examine pharmacy records for documentation of the following: quantity and date of receipt of investigational drug, dispensation and accountability data for drug administration to each patient, loss of materials, contamination, and unused supplies.

4. Record and report (summarize) observations on the progress of the trial and continued acceptability of the facilities; prepare an on-site visit report.
5. Review Investigator files for required documents, (e.g., protocols, protocol amendments etc.), IRB approval of protocols, amendments, Informed Consent, etc., as well as IRB charter and membership, and communications to and from the IRB and Monitor.

Clinical Investigator

A. Institutional Review Board (IRB)

The investigator must assure the Monitor that the IRB:

1. Meets FDA regulations as defined in 21 CFR Part 56 Institutional Review Board (IRB).
2. Has the authority, delegated by the parent Institution and found in the IRB by-laws; operation guidelines; or charter, to approve or disapprove clinical trials and protocols including Informed Consent and other documents (i.e., protocol amendments, information to be supplied to patients concerning Informed Consent, etc).
3. Complies with the proper personnel make-up of the IRB.
4. Convenes meetings using acceptable rules of order for making decisions, records such decisions, and implements them.
5. Files contain: (a) documentation of its decisions as found in IRB minutes and correspondence, (b) written guidelines or by-laws governing IRB functions, (c) protocol, (d) protocol amendments, (e) approved Informed Consent statement and information to be supplied to the patient, and (f) correspondence between IRB and Investigator (i.e., consent changes, protocol amendments, etc.).

B. Informed Consent of Human Patients

The Investigator must assure the Monitor that the Informed Consent for a patient:

1. Meets FDA regulations as defined in 21 CFR Part 50 Informed Consent.
2. Has been approved by the IRB and includes any required information to be given to the patient regarding the trial in which he/she is enrolled including (a) the basic elements and any additional elements necessary and (b) the signature of both the patient and physician on the Informed Consent and that the patient has received his/her copy.

C. Storage and Dispensing of Drug Supplies

The Investigator (or his pharmacist) must assure (demonstrate to) the Monitor that:

1. Adequate and accurate written records showing receipt and disposition of all drug supplies including dates, serial or lot numbers, quantities received, each quantity dispensed, administered, or used with identification of each patient.
2. Purpose and reasons are given in written records for drug disposal, (e.g., the amount contaminated, broken, or lost, etc.) and quantity returned to the Sponsor/CTM supplier.

D. Case Report Forms (CRF)

The Investigator must assure the Monitor that:

1. CRFs, when completed, accurately reflect the medical records on each patient, and
2. CRFs and medical records will be accessible to the Monitor for on-site visits.

E. Files and Records

The Investigator must assure the quality, integrity, and content of his/her files which may be inspected by the Monitor and FDA inspectors. The files must contain, as minimum:

1. Correspondence to and from the IRB and Investigator.
2. Documents that include:
 - a. IRB approved protocols,
 - b. IRB approved protocol amendments,
 - c. IRB approved Informed Consent and information supplied to the patient, and
 - d. IRB charter, membership, and member qualifications.
3. Clinical supplies records that include:
 - a. Records of receipt, date and quantity, batch or lot number,
 - b. Disposition dates and quantity dispensed to each patient, and
 - c. Inventory records.
4. Documents and records must be retained:
 - a. For a period of two years following the date a marketing application is approved for the drug for the indication for which it is being investigated

OR

- b. If no application is to be filed or if the application is not approved for such indication, until two years after the investigation is discontinued and the FDA is notified.

APPENDIX 4

Laboratory Tests

CHEMISTRY	HEMATOLOGY
Total Bilirubin	Hemoglobin
Direct Bilirubin	Hematocrit
Alkaline Phosphatase	RBC
ALT (SGPT)	WBC
AST (SGOT)	Neutrophils
Urea Nitrogen	Bands
Creatinine	Lymphocytes
Glucose	Monocytes
Uric Acid	Eosinophils
Calcium	Basophils
Phosphorus	Platelets
Total Protein	URINALYSIS
Albumin	Color
CK	Specific Gravity
GGT	pH
Sodium	Protein
Potassium	Glucose
Chloride	Ketones
Bicarbonate	Bilirubin
Prolactin	Urobilinogen
LIPID GROUP	Blood
Total Cholesterol	Nitrite
Triglycerides	Microscopic
LDL (Calc)	THYROID GROUP
HDL	Total T4
HEMOGLOBIN A1C	T Uptake
Hemoglobin A1C	TSH
SERUM BETA hCG, QUALITATIVE	HEPATITIS A ANTIBODY
Serum Beta hCG, Qualitative	Hepatitis A Antibody
HEPATITIS B SURFACE ANTIGEN	HEPATITIS B SURFACE ANTIBODY
Hepatitis B Surface Antigen	Hepatitis B Surface Antibody
HEPATITIS C ANTIBODY	HEPATITIS DELTA ANTIBODY
Hepatitis C Antibody	Hepatitis Delta Antibody
PROLACTIN	

Laboratory Tests (continued)

URINE DRUG SCREEN	URINE DRUG SCREEN
AMPHETAMINES - CLASS	PHENOTHIAZINES - CLASS
Amphetamine	Chlorpromazine (Thorazine)
Methamphetamine (Desoxyn)	Perphenazine (Trilafon)
BENZODIAZEPINES - CLASS	Thioridazine (Mellaril)
Alprozolam	Trifluoperazine (Stelazine)
Clorazepate	SEDATIVES AND HYPNOTICS - CLASS
Desalkylflurazepam	Ethchlorvynol (Placidyl)
Diazepam	Ethinamate (Valmid)
Nitrazepam	Glutethimide (Doriden)
Przepam	Meprobamate (Equanil)
Flunitrazepam	Methaqualone (Quaalude)
Oxazepam	Methocarbamol (Robaxin)
Temazepam	Methyprylon (Noludar)
Clonazepam	MISCELLANEOUS AGENTS - CLASS
N-Desmethyldiazepam	Cocaine and/or Metabolites
Flurazepam	Ephedrine/Pseudoephedrine
Lorazepam	Phencyclidine (PCP)
CARDIACS - CLASS	Cannabinoids (THC)
Lidocaine (Xylocaine)	Ethanol
Quinidine/Quinine	SPECIMEN MANAGEMENT (frozen)
NARCOTICS - CLASS	Plasma for Drug Levels
Codeine	Tryptophan Levels
Dihydrocodeine	Large Neutral Amino Acid Levels
Hydrocodone	
Hydromorphone (Dilaudid)	
Meperidine (Demerol)	
Methadone (Dolophine)	
Morphine	
Oxycodone (Percodan)	
Norpropoxyphene	
Pentazocine (Talwin)	
Propoxyphene (Darvon)	