CENTER FOR DRUG EVALUATION AND RESEARCH

ADVISORY COMMITTEE: ENDOCRINOLOGIC AND METABOLIC DRUGS ADVISORY COMMITTEE

DATE OF MEETING: 09/28/95

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SLIDES (BRIEFING PACKAGE)

Endocrinologic and Metabolic Drugs Advisory Committee #60

Food and Drug Administration
Center for Drug Evaluation and Research

September 28, 1995

Parklawn Conference Center, Rooms G, H, I, J
5600 Fishers Lane, Rockville, MD

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FDA REVIEWS and EVALUATION

AGENDA

Endocrinologic and Metabolic Drugs Advisory Committee #60

Food and Drug Administration
Center for Drug Evaluation and Research

DRAFT

September 28, 1995

Parklawn Conference Center, Rooms G, H, I, J
5600 Fishers Lane, Rockville, MD

OPEN SESSION

8:00 Call to Order, Introductions, Opening Comments
Henry G. Bone III, M.D., Chair
Conflict of Interest Statement
Kathleen Reedy, Executive Secretary

8:05 OPEN PUBLIC HEARING

9:05 SPONSOR PRESENTATION
Interneuron Pharmaceuticals Incorporated present
NDA 20-344, Dexfenfluamine Hydrochloride (Redux)

Introduction: Glenn Cooper, MD
Obesity: Need for Treatment:
Mechanism of Action and Clinical Pharmacology:
Richard Wurtman, MD
Efficacy and Safety: Bobby Sandage, Jr., PhD
Neurochemical Effects of large doses of dexfenfluramine:
Robert Moore, MD, PhD
Lack of Abuse Potential: Theodore Cicero, PhD
Special Safety/PPH:
Overall Risk/Benefit: Gerald Faich, MD, MPH
Conclusion: Louis Lasagna, MD

10:50 **Break**

11:00 Guest Expert Speakers

International Primary Pulmonary Hypertension Study:
Lucien Abenhaim, MD, Principal Investigator
Center for Clinical Epidemiology and Community Studies,
Jewish General Hospital, McGill University,
Montreal, Quebec, Canada

11:35 Stuart Rich, MD, IPPH Review Panel
Section of Cardiology, University of Illinois, Chicago

12:00 Neuropharmacology, Neurotoxicity
Lewis Seiden, PhD, University of Chicago

12:25 Mark E. Molliver, MD, Johns Hopkins University

AGENDA

Endocrinologic and Metabolic Drugs Advisory Committee #60

Food and Drug Administration
Center for Drug Evaluation and Research

September 28, 1995

Parklawn Conference Center, Rooms G, H, I, J
5600 Fishers Lane, Rockville, MD

12:50 **Lunch**

2:00 **FDA PRESENTATION**

Leo Lutwak, M.D., Ph.D., Medical Review
Division of Metabolism and Endocrine Drug Products

Ed Nevius, Ph.D., Statistics Review
Statistical Evaluation Branch, Division of Biometrics,
Office of Epidemiology & Biostatistics

Joseph F. Contrera, PhD, Neuropharmacology Review
Division of Neuropharmacology

Bruce Stadel, MD, PhD, Aspects of a Phase IV Study
Division of Metabolism and Endocrine Drug Products

Gloria Troendle, MD, Deputy Director, Summary
Division of Metabolism and Endocrine Drug Products

3:00 **Break**

3:15 Discussion and Questions

5:30 Adjourn

DRAFT

Metabolic and Endocrine Advisory Committee

September 28, 1995

Dexfenfluramine NDA

Dexfenfluramine produces a small mean weight loss with a more substantial loss in a small subgroup of obese patients. The side effects observed in clinical studies are not generally serious or life threatening, and weight loss, if sustained, may result in decreased risk from cardiovascular disease, diabetes, and stroke. However, there are two additional risks that must be evaluated: brain lesions observed in animals and pulmonary hypertension. The brain lesions have no identified clinical correlates and the pulmonary hypertension, while it seems to be definitely drug-related, is apparently quite rare. Dexfenfluramine is the first weight-control drug proposed for indefinite administration and, as such, presents unique challenges in evaluating the benefits (weight loss that is small or limited to a small subgroup) and the potential risks.

Questions:

1. Is the evidence of efficacy sufficient to warrant approval of dexfenfluramine for long-term (indefinite) use as proposed?

2. Is the evidence of safety sufficient to warrant approval for long-term use as proposed?

3. a. Should a large, simple, at least 2 year, randomized trial be required to provide information on weight, mortality, and serious morbidity (heart disease, diabetes, strokes)?

   b. If "yes" should the trial be a requirement for approval or a phase 4 commitment?

4. Are there any issues the committee would like to see addressed in labeling?

MEDICAL OFFICER'S REVIEW OF NDA AMENDMENT

NDA NO. 20-344; AMENDMENT NO. 19
GENERIC NAME: DEXFENFLURAMINE HYDROCHLORIDE CAPSULES
TRADE NAME: REDUX®
SPONSOR: Interneuron Pharmaceutical Inc.
One Lodgement Center
99 Harden Ave., Suite 340
Lexington, MA 02173
Tel: (617) 861-8444
Fax: (617) 861-3830

DATE SUBMITTED: 05/12/95
DATE RECEIVED, CDER: 05/15/95
DATE RECEIVED, M.O.: 05/18/95
DATE OF M.O. REVIEW: 05/18/95 to 09/15/95

This submission, consisting of 8 volumes, is in response to the FDA letter of Feb. 17, 1995, which was a "non-approvable" letter. The Sponsor, however, is treating that letter as one containing questions to be answered. Although this submission is listed as an Amendment, it is actually a resubmission of the NDA.

I. CHEMISTRY
The Chemistry problems discussed will be reviewed by the Reviewing Chemist.

II. PHARMACOLOGY
The Pharmacology issues are both clinical and preclinical and will be considered in part here.

A. Toxicology Study in Monkeys (To be reviewed by Contrera)

B. Positron Emission Tomography Study in Humans (See also under CLINICAL)

C. Tumor Data for Carcinogenicity Studies (To be reviewed by Division Pharmacologist)

III. BIOPHARMACEUTICS
To be reviewed by Biopharmaceutics Division.

IV. CLINICAL

A. Primary Pulmonary Hypertension
An independent epidemiologic study (International Primary Pulmonary Hypertension

Study, or IPPHS) was conducted by Prof. Lucien Abenhaim and associates in five countries (France, the United Kingdom, Belgium, the Netherlands, and Switzerland) using a case-control technique, between September 1992 and September 1994. The initial report of this study is included in this submission; this consists primarily of conclusions and does not contain original case reports. It has been analyzed by Dr. Bruce Stadel. His consultation is appended as part of this review.

To summarize, the IPPHS was a case control study. Because of recruitment and eligibility requirements, four countries (no cases were reported from Switzerland) were included in the final study which was designed to evaluate the effects of dexfenfluramine and other anorexigenic drugs on the occurrence of PPH. The main findings were that:

(1) Persons who had used anorexigenic agents for longer than 3 months were about 9 times more likely to have PPH than those who had never used these drugs.

(2) The increased risk of PPH was seen in those who had used these agents within the year before being studied. There was no significant increase in risks in those who had stopped the agents more than one year before the study.

(3) Those with BMI $\geq$ 30 at some time in their lives were about 2-4 times more likely to have PPH than those at lower BMI.

(4) The use of anorexigens was associated with a similar risk in those with BMI $\geq$ 30 or $<$ 30, indicating that the drugs were an independent risk.

(5) The results represent the risks for dexfenfluramine primarily, since this was the principal drug used.

The principal weakness of the study was that the sex and age distribution of the cases was not shown.

The conclusion is that the absolute incidence of PPH is sufficiently low that the risk associated with anorexigen use is low.

B. Neurotoxicity Studies

1. The Sponsor states that they have been unable to confirm the finding of neurotoxicity in animals. They support this with an extensive review of the literature and of their studies, concluding that the depressed levels of serotonin content of axons produced by high pharmacologic doses of dexfenfluramine result in lack of visualization of fine fibers by immunofluorescence, but these findings

return to normal with time. The doses producing these changes in animals result in higher brain concentrations than those measured in obese volunteers following chronic administration of dexfenfluramine and are thus unlikely to occur in clinical use.

2. Human MRS Study (IP94-006)

This was an open-label, repeated measures design study to estimate the brain concentration of d-fenfluramine and its fluorinated metabolites by ^{19}F magnetic resonance spectroscopy (MRS) in 12 obese women treated with 15 mg dexfenfluramine twice daily for up to 90 days, with estimates obtained at 1, 10, 60, and 90 days of treatment. The subjects were 48.5 ± 5.2 years of age weighed 86.2 ± 8.6 kg and had BMI of 32.2 ± 2.8

11 subjects completed the 90 day study; one discontinued because of hospitalization for right lower quadrant pain. Adverse experiences reported included headache (in 50%) and diarrhea (in 25%). Efficacy was not an end-point; the 11 patients lost an average of 19 lb in the 90 days.

Validation of the ^{19}F MRS procedure was validated for precision, accuracy, selectivity, and sensitivity using standard solutions.

Although ^{19}F MRS has been used to estimate brain concentrations in humans of fluorine containing drugs such as fluoxetine, no validation studies have been done correlating the MRS data with standard gas chromatographic (GC) procedures in animal studies. In the present study, 3 rhesus monkeys were dosed with 5.0 mg/kg sc bid of dexfenfluramine for 11 doses, scanned by ^{19}F MRS, received one additional dose, and sacrificed 2 hours later for plasma and brain analyses by GC of dexfenfluramine and d-norfenfluramine. The mean total concentration of drug and metabolite in the monkey brain by ^{19}F MRS was 155.37 ± 47.5 μM; this was corrected for the 53.1% of the monkey head volume which is not brain to 133.40 ± 44.52 μM. The postmortem GC analyses showed a much lower value, 71 ± 11.8 μM.

The studies in the 11 subjects are summarized in the table below. After the first 2 doses, brain concentrations of DF plus d-NF were below 2 μM, the lower limit of quantification by this method. Steady state was achieved on day 10, with no significant increases noted on days 60 and 90, leading the conclusion that no accumulation of these compounds occurs with continuing treatment. Plotting of brain/plasma ratio of fluorinated compounds against brain and plasma concentra-

tions suggest that there is only a slight increase in the brain concentration with increasing plasma concentration and a decrease in the ratio with increasing plasma concentration, indicating a saturable mechanism for transfer of drug into the brain.

TABLE I
BRAIN AND PLASMA CONCENTRATIONS
(Total μM of Dexfenfluramine and d-Norfenfluramine)
(Mean ± SD)

DAY	BRAIN	BLOOD
1	< 2	0.09 ± 0.002
10	3.9 ± 1.9	0.23 ± 0.08
60	4.1 ± 0.7	0.27 ± 0.08
90	4.5 ± 0.9	0.25 ± 0.08

MEDICAL OFFICER'S ASSESSMENT:
The ^{19}F MRS technique used in this study is a research tool and its clinical applicability has not been validated. The results, however, offer support for the concept of non-accumulation of drug with duration of use and of concentrations well below those that produced neurotoxicity in experimental animals. Although the number of subjects was small, the small standard deviation offers a degree of comfort concerning the safety of this drug.

3. Human PET Studies

a. Study S 5614; C-5614-035-FRA: Study of $5HT_2$ receptors by positron emission tomography after chronic treatment (3 months) with dexfenfluramine in obese volunteers.

After a 2-3 week single blind placebo run-in phase, 15 obese subjects (120-180% of ideal weight) (6 receiving placebo, 5 female, 1 male; 9 receiving 15 mg twice daily of dexfenfluramine, 6 female, 3 male) were placed on a randomized double-blind 3 month study followed by a 1 month single blind placebo run-out. PET scan was performed of ^{18}F-setoperone-labeled $5HT_2$ receptors on days 0 and 120 of the study. There was greater weight loss on dexfenfluramine than on placebo ($p=0.014$). No significant intergroup difference was seen between the two scans in the neocortex/cerebellum ratio at 50-120 minutes after radioligand injection. PET data were available in 10 subjects (5 per group).

b. Study S 5614; C-5614-037-BEL: Study of the central serotonergic system using positron emission tomography in patients treated with dexfenfluramine.

Three months of treatment with dexfenfluramine 15 mg twice a day for 2 weeks followed by 30 mg/day for 2.5 months in 8 healthy young male volunteers between 120 and 150% of ideal body weight resulted in significant weight loss. Positron emission tomography studies with labelling of 5-HT_2 receptors by ^{18}F-altanserine were performed before treatment and 15 days after the last dose of dexfenfluramine; no changes were seen in cortical receptors.

MEDICAL OFFICER'S ASSESSMENT

PET is an experimental tool; in these studies, the data support the thesis of lack of effect of dexfenfluramine on serotonergic receptors at doses used for production of weight loss.

V. UPDATED POST-MARKETING SAFETY REPORT

A. PULMONARY HYPERTENSION

A total of 100 cases of pulmonary hypertension have been reported in post-marketing surveillance between August 1984 and December 1994. Of these reports, 14 resulted in death. There were six patients who underwent lung transplantation (one of whom died). These cases will be summarized in Table II, to be submitted as a supplement to this review with additional analysis.

VI. DRAFT LABELLING

This will be reviewed separately, based on final decisions concerning approvable/nonapprovable status of this application.

APPEARS THIS WAY
ON ORIGINAL

Leo Lutwak, M.D., Ph.D.
September 15, 1995

cc: NDA Arch.
HFD-510
HFD-510/GTroendle/LStockbridge/AJordan/LLutwak

Gloria Troendle 9-15-95

I N T E R O F F I C E M E M O R A N D U M

DATE: 8 September 1995

FROM: Bruce V. Stadel, MD, MPH
Medical Officer/Epidemiology Bruce V Stadel

SUBJECT: NDA # 20-344/Dexfenfluramine/Interneuron Pharmaceuticals, Incorporated
Amendment #019/ Part IA/International Primary Pulmonary Hypertension Study

To: Leo Lutwak, MD, PhD
Medical Officer/Metabolism & Endocrine Group #1

This replies to your request for consultation regarding the International Primary Pulmonary Hypertension Study (IPPHS). My review is based on the IPPHS study report contained in the NDA submission cited above, and information obtained directly from the Chairman of the IPPHS Scientific Board, Professor Lucien Abenhaim, McGill University, Canada. I will first summarize the background, methods, and results of the study, then comment on the methodology and clinical interpretation, and close with conclusions and recommendations.

BACKGROUND

The IPPHS was a case-control study designed to evaluate the effect of using dexfenfluramine (DF) or other anorexigens on the occurrence of PPH. It carried out in France, Belgium, the Netherlands, and the United Kingdom, and was paid for by the Servier Pharmaceuticals. I think Servier was motivated to fund the study by the French Agence du Medicament because of adverse drug experience reports associating DF use with PPH, and that the money was managed at McGill after it left Servier, although these issues are not discussed in the NDA submission. However, it is noted in the submission that the Medical Research Council of Canada peer-reviewed the study and approved the funding under the "MRC-Industry" Program, and that the Ministry of Public Health and Environment in Belgium also expressed support for the study.

The IPPHS was largely developed, managed, and analyzed by a Coordinating Center at McGill which consisted of four persons: Professor Abenhaim, for overall direction; Dr. Yola Moride, for protocol development, coordination of field work, the interim analysis, and creation of the database; Dr. Thierry Ducruet, for performance of statistical analyses; and Dr. Jacques Benichou, a consultant from the U.S. National Cancer Institute. There were Local Research Teams in the four countries for case and control recruitment, an Expert Review Panel for judging the eligibility of PPH cases to be included in the analyses, and a Scientific Board for scientific oversight and review of the final report.

METHODS

A matched study design was used because many of the PPH cases were identified at specialized referral centers. Under these conditions, the matching of controls to each case according to the practice of the case's general practitioner (GP) is an appropriate method for ensuring that persons in the resulting case-control sets had the same general opportunity, in the past, for having been prescribed DF or other anorexigens. In addition to matching on GP, the controls were also matched to the cases for sex, age (+/- 5 years), and number of physician visits per year. Overall, four controls were sought for each case, but fewer or more controls per case were permitted depending on availability. If controls for a case could not be found at the practice of the case's GP, they were sought at the practice of another GP in the same geographic area. The basic inclusion criteria for both cases and controls were: age 18-70 years, both sexes, resident of the country for more than six months, interview possible, consented to participate, and not suffering from active chronic disease (cancer, systemic diseases, etc.)

Cases. PPH cases were defined as men or women 18-70 years of age who received a first diagnosis of PPH between 1 September 1992 and 30 September 1994. The date of diagnosis was defined as the date of first right heart catheterization, and cases were retained in the final analyses only if documentation of the diagnosis was considered definitive by the Expert Review Panel. In total, 298 possible PPH cases were identified, of which 95 (32%) were retained in the final analyses. Of the 203 (68%) possible cases that were excluded, 137 (67%) either did not meet the basic inclusion criteria for cases and controls or the specific criteria for defining cases. The remaining 66 (33%) were excluded because they died before interview (26), were found not to have definite PPH by the Expert Review Panel (23), or could not be studied within the time available, were lost to follow-up, or refused to participate (17).

Controls. Controls were matched to the cases as described above, and an "index date" was assigned to each control, corresponding to the date of diagnosis for the matching case. In total, 492 potential controls were interviewed, of which 355 (72%) were retained the final analyses. The other 137 potential controls were excluded because they were matched to possible cases that were excluded as described above.

Interviews. Cases and controls were interviewed by specially trained interviewers who were not told about the specific aims of the study, to obtain information about: (1) socio-demographic and personal characteristics, medical and surgical history, familial medical history, habits, exposure to high pressure and high altitude, and other general information; (2) a detailed history of drug use during the 3-4 years prior to interview.

This was obtained using a calendar method for recording data, and a visual display of packages and/or tablets for commonly prescribed drugs. Use of DF and other anorexigens was recorded in the same way as use of other drugs.

Analysis. Standard methods for bivariate and multivariate analysis of matched case-control data were used. The main outcome statistics are odds ratios (ORs) for the association between PPH and the use of DF or other anorexigens, with 95% confidence intervals (CIs). For a rare disease such as PPH, these odds ratios are accurate estimates of the relative risk, which is the risk of PPH in persons who used DF or other anorexigens divided by the risk in persons who did not use these drugs. Initially, bivariate analyses were done for DF or other anorexigens, and many additional variables that might be risk factors for PPH. Subsequently, multivariate analyses were done which included DF, other anorexigens, and the additional factors that were found to associated with PPH in the bivariate analyses: Quetelet Body Mass Index (BMI) $\geq$ 30 at least once in lifetime, a history of treated hypertension, a history of smoking at least four years before interview, and a history of having tried to lose weight using several methods other than DF or other anorexigens.

RESULTS

The main findings are that:

(1) Persons who had used DF or other anorexigens for longer than three months were about nine times more likely to have PPH than persons who had never used these drugs (OR= 9.1, 95% CI= 2.6-31.5). There was no significant increase in risk among persons who had used the drugs for three months or less (OR =1.9, 95% CI= 0.5-6.9).

(2) The increased risk of PPH was concentrated in persons who had used DF or other anorexigens within the year before being studied (OR= 5.9, 95% CI= 2.1-16.9). There was no significant increase in risk among persons who had stopped using the drugs more than one year before being studied (OR= 2.4, 95% CI= 0.6-8.8).

(3) Persons with BMI$\geq$ 30 at least once in their lives were about 2-4 times more likely to have PPH than persons with BMI< 30 (among never-users of DF or other anorexigens, OR= 2.1, 95% CI= 1.0-4.2; among ever-users, OR= 3.6, 95% CI= 1.3-9.8).

(4) The use of DF or other anorexigens was associated with a similar relative increase in the risk of PPH among persons with BMI≥ 30 (OR= 5.0, 95% CI= 1.5-16.2) and among persons with BMI< 30 (OR= 2.9, 95% CI= 1.1-7.4). Thus, the effect of using DF or other anorexigens was to multiply the effect of having a BMI ≥ 30, so that the effect of the two risk factors together was greater than the sum of their individual effects.

(5) The results described above pertain mainly to DF, since most use of "DF or other anorexigens" by cases and controls in the study was in fact use of DF. However, the results for other anorexigens were similar to the results for DF to the extent that separate analyses were feasible.

COMMENT

The IPPHS is an excellent study, and I think it provides the best resource we can expect to obtain for information about the effect of using DF or other anorexigens on the occurrence of PPH. I will comment on specific strengths and weaknesses of the study with regard to methodology and to clinical interpretation.

Methodology

Very careful consideration is given in the IPPHS study report to the main sources of potential error in case-control studies, which are selection bias, information bias, confounding, and chance. In this regard, I think many of this issues raised in the commentary by Dr. Gerald Faich that is included in the NDA submission are in fact adequately discussed in the IPPHS study report itself, and are not sufficient reasons to discount the findings. I do agree with Dr. Faich that it would be helpful to see a comparison of findings about the use of DF or other anorexigens for controls drawn from the practice of the matched case's GP versus controls drawn from the practice of another GP in the same geographic area, and that it would also be helpful to see ORs with BMI stratified at 27 instead of 30 (since this may be an issue with regard to proposed labeling), but I doubt that these analyses will appreciably change the overall study findings. Also, I think Dr. Faich oversimplifies a complex topic in stating that "Odds ratios below 5 in pharmacoepidemiologic studies are often only suggestive..." due to the potential for bias or confounding. In my own experience, the consistency and plausibility of findings from studies in the area of pharmaco-epidemiology have depended more on the size and quality of the studies, than on the ORs themselves.

Clinical Interpretation

The IPPHS report does not provide a tabulation of data on the use of DF or other anorexigens, by the cases and controls, according to country, sex, and age. I think this information is needed for clinical/regulatory interpretation of the IPPHS findings, and I therefore asked Professor Abenhaim, on 15 August, if he could provide me the tabulation referred to above. He was very courteous and faxed me the requested data on 30 August. These data are summarized in Tables 1-3, and are interpreted below.

Table 1 shows that:

(1) A total of 20 (21.1%) of the 95 PPH cases and 23 (6.5%) of the 355 controls in the final IPPHS analyses had used DF or other anorexigens.

(2) However, only 2 (6.9%) of the 29 male cases and 1 (1.1%) of the 90 male controls had used DF or other anorexigens, compared to 18 (27.3%) of the 66 female cases and 22 (8.3%) of the 265 female controls.

(3) Thus, the main findings from the IPPHS about the effect of using DF or other anorexigens on the occurrence of PPH are, in essence, findings about the effect in women.

Table 2 shows that:

(1) As above, 18 (27.3%) of the 66 female PPH cases and 22 (8.3%) of the 265 female controls had used DF or other anorexigens.

(2) However, only 1 (7.7%) of the 13 female cases and none of the 45 female controls in the U.K. & Netherlands had used DF or other anorexigens, compared to 15 (33.3%) of the 45 female cases and 19 (10.6%) of the 180 female controls in France, and to 2 (25.0%) of the 8 female cases and 3 (7.5%) of the 40 female controls in Belgium.

(3) Thus, the main findings from the IPPHS about the effect of using DF or other anorexigens on the occurrence of PPH are, in essence, findings about the effect for women in France and Belgium.

Table 3 shows that:

(1) A total of 17 (32.1%) of the 53 female PPH cases and 22 (10.0%) of the 220 female controls in France and Belgium had used DF or other anorexigens.

(2) The female cases and controls in France and Belgium were distributed across the entire 5-decade age interval of eligibility for cases, from 18 through 70 years.

(3) The association between PPH and the use of DF or other anorexigens appears to be concentrated in women over 40 years of age, (However, this observation is tentative, since it does not take into account the matched design of the IPPHS.)

CONCLUSIONS AND RECOMMENDATIONS

I think the IPPHS provides strong evidence that the use of DF or other anorexigens by women for over three months increases their risk of developing PPH, and that this increased risk persists for up to a year after the drugs are discontinued. I also think the IPPHS provides evidence that the effect of using DF or other anorexigens on the risk of PPH acts in a way that multiplies the effect of having a BMI $\geq$ 30, such that the combined effect of the two factors together is greater than the sum of their individual effects. These adverse effects of using DF or other anorexigens may be greater for women over 40 years of age than for younger, women, but this observation is tentative. Finally, since most of the exposure to "DF or other anorexigens" in the IPPHS was in fact exposure to DF, I think the above conclusions can be reasonably applied to decision-making about DF itself.

I recommend that Professor Abenhaim be invited to present the findings of the IPPHS to the Metabolic-Endocrine Drugs Advisory Committee meeting on 29 September, and have asked the Executive Secretary of the Advisory Committee to do this. As part of his presentation, I will ask Professor Abenhaim to:

(1) Describe the IPPHS data concerning the use of DF or other anorexigens by controls drawn from the practice of the matched case's GP versus controls drawn from the practice of another GP in the same geographic area, and discuss the implications of any differences between the two types of controls with regard to the overall validity of the study.

(2) Describe any effects on the main findings from the study if BMI is stratified at 27 instead of 30, since this may be an issue with regard to proposed labeling.

(3) Show how the PPH case and controls who had used DF or other anorexigens for longer than three months were distributed by duration of use, e.g., >3 months to $\leq$ 1 year, 1-2 years, and so on. As Dr. Troendle has pointed out, this would help to provide perspective on what is actually meant by "longer than three months" of use.

(4) If possible, use available data on the total incidence of PPH in France and/or Belgium, and data from the IPPHS, to estimate the absolute risk of PPH that is attributable to the use of DF or other anorexigens by women 18-70 years of age, according to the following definitions and method of calculation:

Definitions

I_T = Total incidence of PPH in France and/or Belgium, per 100 000 women 18-70 years of age per year, in 1993-94.

I_E = Incidence of PPH in France and/or Belgium, per 100 000 women 18-70 years of age per year, in 1993-94, for women who had used DF or other anorexigens for longer than three months within the year before diagnosis.

I_U = Incidence of PPH in France and/or Belguim, per 100 000 women 18-70 years of age per year, in 1993-94, for women who had never used DF or other anorexigens.

P = Proportion, in the IPPHS database, of female controls 18-70 years of age, in France and Belgium, who had used DF or other anorexigens for longer than three months within the year before their "index dates."

OR = Odds ratio, based upon the IPPHS data, for the association between the occurrence of PPH and the use of DF or other anorexigens for longer than three months within the year before the date of diagnosis (cases) or the "index date" (controls).

AR = Attributable risk = $I_E - I_U$

Calculations

$I_T = I_E P + I_U (1-P)$

$I_T = (OR)\ (I_U)\ P + I_U (1-P)$

$I_U = I_T / (OR)\ P + (1-P)$
Put in values of I_T, OR, and P, and solve for I_U

Then $I_E = (OR)\ I_U$, and

$AR = I_E - I_U$

cc
NDA 20-344
HFD-510/SobelS/TroendleG/StadelB
HFD-007/KleinM/KramerD

APPEARS THIS WAY
ON ORIGINAL

APPEARS THIS WAY
ON ORIGINAL

TABLE 1

Cases and controls
by
sex and use of DF or other anorexigens

BOTH SEXES

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	20	(21.1)	23	(6.5)
	No	75	(78.9)	332	(93.5)
		95		355	

MEN

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	2	(6.9)	1	(1.1)
	No	27	(93.1)	89	(98.9)
		29		90	

WOMEN

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	18	(27.3)	22	(8.3)
	No	48	(72.7)	243	(91.7)
		66		265	

TABLE 2

Female cases and controls
by
country and use of DF or other anorexigens

ALL FOUR COUNTRIES

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	18	(27.3)	22	(8.3)
	No	48	(72.7)	243	(91.7)
		66		265	

U.K. & NETHERLANDS

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	1	(7.7)	0	(0.0)
	No	12	(93.1)	45	(100.0)
		13		45	

FRANCE

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	15	(33.3)	19	(10.6)
	No	30	(66.7)	161	(89.4)
		45		180	

BELGIUM

		Cases N	(%)	Controls N	(%)
Had used DF or other anorexigens	Yes	2	(25.0)	3	(7.5)
	No	6	(75.0)	37	(92.5)
		8		40	

TABLE 3

Female cases and controls in France and Belgium
by age and percent that had used DF or other anorexigens

Age (Years)	Cases N	Cases (% users)	Controls N	Controls (% users)
≤30	9	(11.1)	35	(17.1)
31-40	10	(10.0)	47	(8.5)
41-50	17	(64.7)	65	(13.8)
51-60	11	(27.3)	37	(5.4)
>60	6	(16.7)	36	(2.8)
	53	(32.1)	220	(10.0)

Statistical Review and Evaluation

MAY 6 1994

NDA#: 20-344/Class 3S

Applicant: Interneuron Pharmaceuticals Incorporated

Name of Drug: Dexfenfluramine Hydrochloride Capsules

Indication: Adjunct Management of obesity in patients in a supervised program

Document Reviewed: Vols. 1.1, 326-540
Submission dated May 24, 1993

Background:

Institute de Recherches Internationales Servier, of France, initiated clinical development of dexfenfluramine in Europe. Dexfenfluramine is an active component of fenfluramine (Pondimin) which was approved (NDA 16-618) in 1973 indicated for management of exogenous obesity as a short-term (a few weeks) adjunct in a regimen of weight reduction based on caloric restriction. In February 1990, Interneuron Pharmaceuticals Incorporated licensed the commercial rights to develop and market dexfenfluramine in the United States from Servier. Portions of this NDA have been used by Servier to obtain marketing approvals in various countries, including the United Kingdom, France, Italy, Switzerland and Australia.

The action of dexfenfluramine in treatment of obesity is primarily via decreased caloric intake associated with increased serotonin levels in brain synapses.

A total of 17 double-blind, placebo-controlled trials (including dose-response Study No. IP92-003) were conducted with dexfenfluramine in obese patients between 110% and 180% of their ideal body weight. The objective of these studies was to assess the efficacy and safety of the drug when compared to placebo.

Three of the 17 studies were selected by the sponsor as "pivotal" trials. Noble and IP92-003 were United States studies, and INDEX was a multinational study. The Noble study was a single-center study and the other two were multicenter studies. The treatment duration was 6 months for the Noble study, 3 months for study IP92-003 and 12 months for the Index study.

The sponsor stated that in a meeting between the FDA and Interneuron on August 20, 1991, it was agreed that the primary efficacy parameter was the absolute change from baseline in body weight using the last-value-carried-forward method of analysis. Secondary efficacy parameters were absolute change from baseline in body weight using patients continuing in the study, and percent change from baseline in body weight using initial weight and amount overweight, for both populations (LOCF and completers).

I. Nobel Study

The objective of the study was to determine efficacy of dexfenfluramine in obese patients who have lost weight.

This single-center, randomized, double-blind, placebo-controlled 24-week study enrolled a total of 60 patients (30 drug, 30 placebo). Patients were eligible if they were physically and psychologically healthy, had lost at least 10 pounds (4.5 kg) during the past year, had not lost any weight during the past month, and weighed at least 10% over their ideal body weight. Dosing schedule was either dexfenfluramine 15 mg BID or matching placebo. Patients were placed on standardized, calorie-restricted diets during the trial. The 24-week trial consisted of a baseline visit and 7 follow-up visits of weeks 1, 2, 4, 8, 12, 16, and 24.

Diet

The standardized diet included 1200 calories per day for women and 1500 calories per day for men. Evaluations during the study included 1. body weight, 2. eating behavior 3. adverse events.

Dosing Regimen

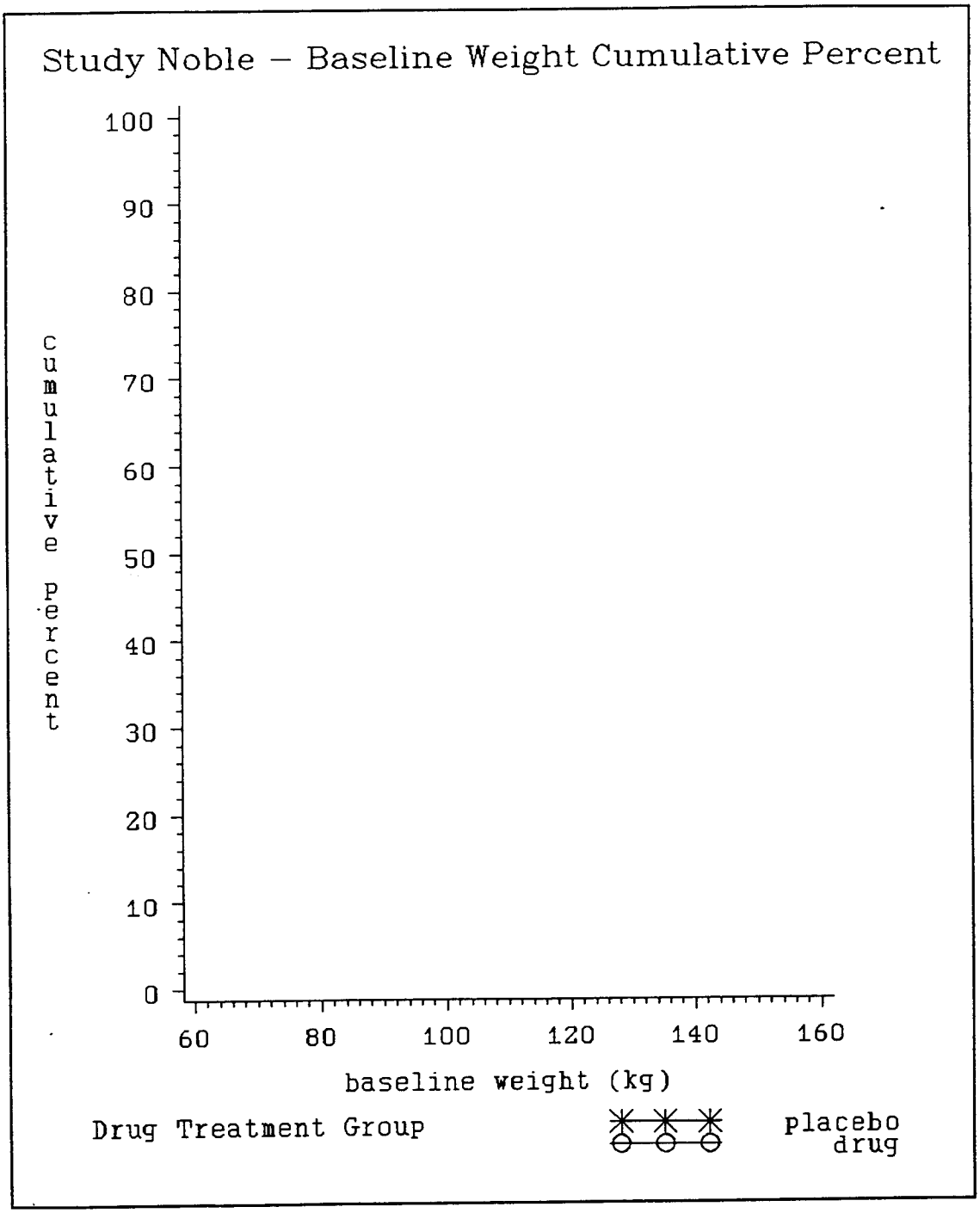
For the first 3 days of the study, patients received one dose per day of 15 mg drug or placebo with breakfast. From Day 4 to the end of the trial, patients received either 15 mg drug or placebo twice a day, one dose in the morning and one in the evening with meals.

Demographics

The baseline characteristics were not statistically significantly different between the two treatment groups in age, ethnic origin, height, weight, body mass index, tobacco habit, alcohol usage, time of onset of obesity duration of obesity or familial history of obesity. The only statistically significant difference between the two treatment groups was that placebo patients had attained a higher mean maximum adult weight than dexfenfluramine patients (110.1 kg vs. 97.1 kg, respectively, p=0.0389).

For randomized patients (30, drug, 30, placebo), the mean baseline body weight was 93.2 kg in the drug group and 100.2 kg in the placebo group. So, on the average, patients on placebo were 7kg heavier than patients on drug at baseline although not significantly different. Figure 1 is the cumulative percentage distribution of the baseline weight of the two treatments. This figure illustrates, for example, that 40% of the drug patients weighed less than 80 kg at baseline compared to only 22% of the placebo patients.

ig 1. Percent Distribution of Baseline Weight by Treatment



The mean baseline weights in kilogram by gender and drug are as follows:

	Placebo	Drug
Male	104.0(n=9)	96.1(n=4)
Female	98.6(n=21)	92.8(n=26)

Placebo had more male patients than the drug group (9 vs. 4) and both male and female patients in the placebo group on the average weighed more than patients in the drug group.

Patient Disposition

Of the 60 randomized patients, 18 (30%) withdraw early. The reason for termination and last weight visit are in Table I.

Table I. Patient Withdrawal by Treatment

Treatment	Patient	Last Weight Visit	Reason for Termination
Drug	5	Baseline	Adverse Event
	11	Week 12	Lost to Follow-up
	17	Week 1	Lost to Follow-up
	18	Week 8	Lost to Follow-up
	21	Week 8	Lost to Follow-up
	24	Week 8	Lost to Follow-up
	29	Week 2	Adverse Event
	46	Week 4	Adverse Event
	49	Week 4	Lost to Follow-up
	56	Week 2	Adverse Lab Experience
	60	Baseline	Lost to Follow-up
Placebo	6	Baseline	Non-compliance
	8	Week 8	Intercurrent Event
	22	Baseline	Adverse Event
	31	Baseline	Lost to Follow-up
	44	Week 2	Adverse Lab Experience
	48	Week 2	Lost to Follow-up
	59	Week 2	Adverse Lab Experience

Five patients (2 drug and 3 placebo) withdrew before post baseline efficacy evaluations. A total of 55 patients (28 drug and 27 placebo) were in the efficacy evaluation. Of those, 13 patients (9 drug and 4 placebo) withdrew prematurely. A total of 42 patients (19 drug and 23 placebo) completed the study. Patients disposition is as follows:

Table II. Patient Disposition

Patient Disposition	Drug	Placebo	Total
Randomized	30	30	60
Week 1 Dropout	2	3	5
Evaluable for Efficacy	28	27	55
Dropout After Week 1	9	4	13
Completed Study	19	23	42

Deviations from Protocol

Patients taking the drug missed more treatment days than patients taking placebo. At Week 16, 42% (8/19) patients in the drug group compared with 9% (2/23) of the placebo patients missed at least one day of treatment which was statistically significant (p=0.01).

For returned capsules, at Week 8 and Week 12 patients in the drug group returned significantly fewer capsules than those in the placebo group. The sponsor noted that if no bottle was returned, zero was used as the number of capsules returned for that patient.

Sponsor's Analysis

For efficacy population (28,drug, 27, placebo), analysis of weight, change of weight from baseline, percent change of baseline weight, percent change of initial baseline overweight were performed on last observation carried forward as well as on observations at each visit using ANOVA. The last observation carried forward results for weight in kilogram, change of weight and percent change of baseline weight are as follows:

Table III Patient Weight, Absolute Weight Change and % Change by Visit (LOCF)

Visit		Weight	Change from baseline	% Change from baseline
Baseline	Drug Placebo	93.1(21.6)* 99.4(18.1) p=0.25		
Week 1	Drug Placebo	91.9(21.5) 99.0(18.0) p=0.19	-1.2(1.4) -0.4(1.4) p=0.02	1.4(1.5) 0.4(1.4) p=0.01
Week 2	Drug Placebo	91.1(21.4) 98.1(18.0) p=0.19	-2.1(1.5) -1.3(1.3) p=0.05	2.3(1.7) 1.3(1.4) p=0.02
Week 4	Drug Placebo	90.2(21.1) 98.1(17.8) p=0.14	-3.0(1.9) -1.3(2.0) p<0.01	3.2(2.0) 1.3(1.8) p<0.01
Week 8	Drug Placebo	89.5(21.5) 97.8(17.8) p=0.13	-3.6(2.5) -1.6(3.1) p=0.01	4.0(2.7) 1.6(2.9) p<0.01
Week 12	Drug Placebo	89.0(21.9) 98.0(17.8) p=0.10	-4.1(2.9) -1.4(4.5) p=0.01	4.6(3.3) 1.3(4.3) p<0.01
Week 16	Drug Placebo	88.7(21.9) 97.2(17.6) p=0.12	-4.4(3.7) -2.2(5.0) p=0.07	4.9(4.1) 2.1(4.4) p=0.02
Week 24	Drug Placebo	88.3(21.8) 97.1(17.7) p=0.11	-4.9(4.5) -2.3(6.7) p=0.10	5.3(4.8) 2.1(6.0) p=0.03

* standard deviation

The sponsor noted that variability in the placebo group exceeded the mean in the last three timepoints (Weeks 12, 16, and 24). One placebo patient (No. 19) lost 21 kg and the next greatest weight loss in each group was approximately 13 kg. Because of this differential in variation between the treatment groups, a post-hoc non-parametric analysis was conducted to minimize the effect of outliers. In this analysis of the absolute weight change from baseline, dexfenfluramine patients lost statistically significantly more weight than did placebo patients at all timepoints ($p<0.05$).

For mean change from baseline the observed cases results for week 1 to week 12

were similar to the last observation carried forward. The mean and standard deviation for week 16 were -5.5(3.8) for the drug group with n=19, and -2.4 (5.4) for the placebo group with n=23. For week 24, it was -6.1(4.8), drug versus -2.6(7.2), placebo with a p-value of 0.07. Sample size was unchanged from week 16.

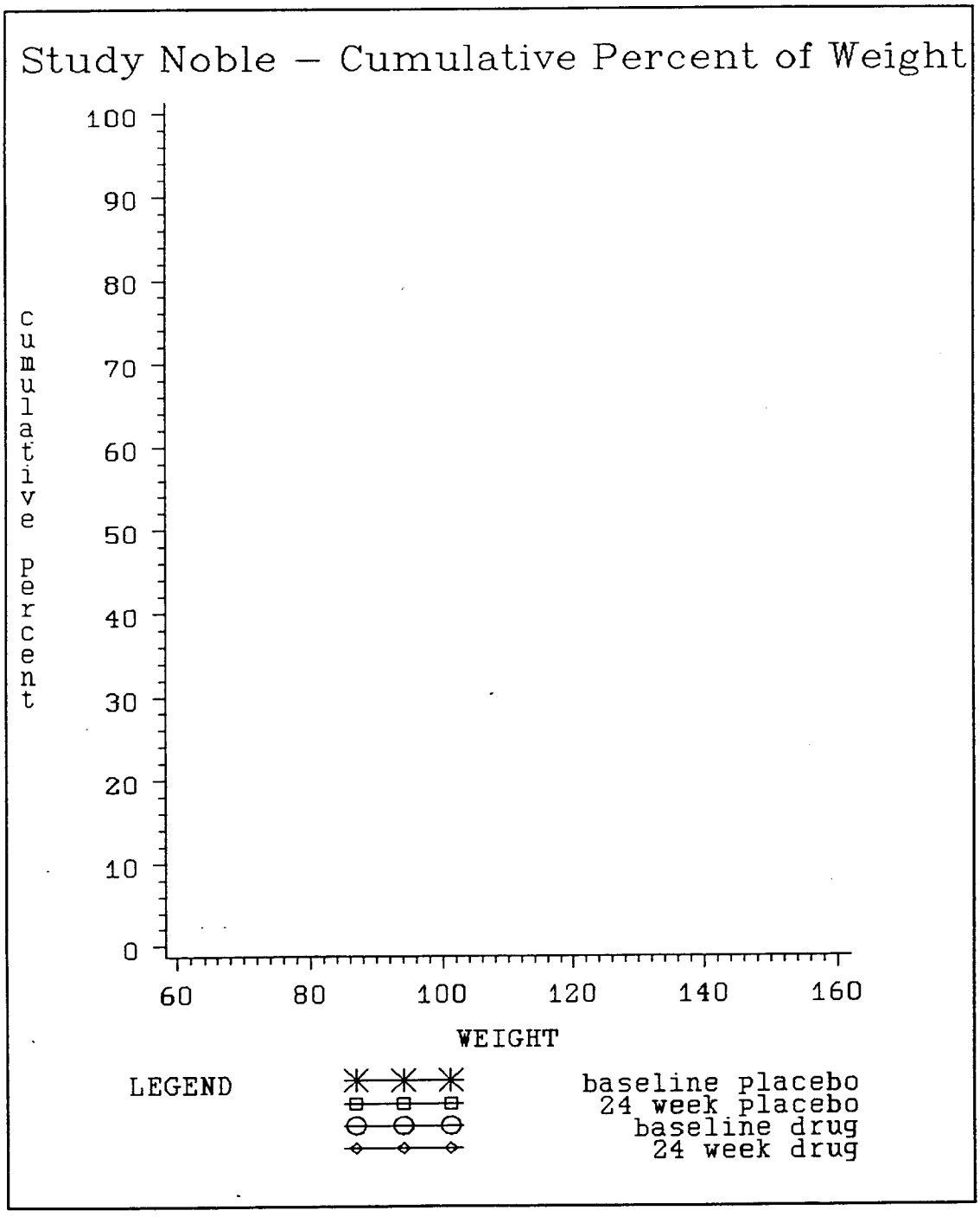
The sponsor performed analysis of covariance on weight change from baseline with the baseline weight as the covariate. But the sponsor stated that "The assumption test for parallelism (equal slopes for the two treatment groups) was not rejected. However, a statistically significant linear relationship between the change from baseline (last value carried forward) and the baseline weight was not detected for any post-baseline visit. Since both statistical assumptions necessary for the model were not achieved, the least squares adjusted means and the associated p-values are not presented." It is unclear how the sponsor determined it is not "statistically significant" for the linear relationship between the weight change from baseline and baseline weight. One way to check is the absolute value of the correlation between covariate and the dependent variable if it is less than 0.3, ANCOVA might not be useful. The weight and baseline weight should be highly correlated.

For appetite and carbohydrate craving evaluations, there were no statistically significant differences between drug and placebo in any of the visits.

Reviewer's Analysis:

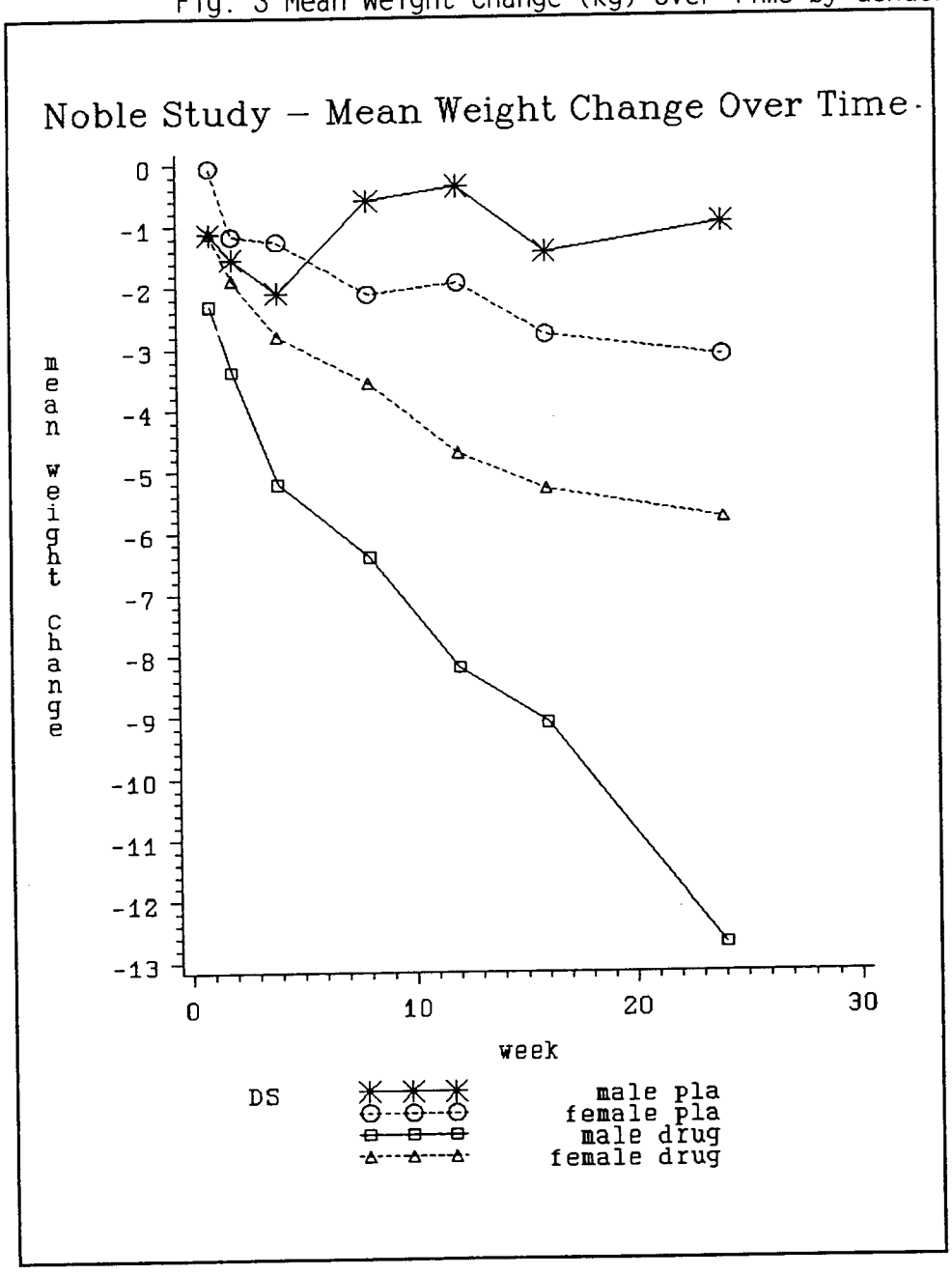
The percent cumulative distribution of patient weight at baseline and week 24 is in Fig 2. Note the shift between baseline and week 24 for drug patients contrasted with similar baseline and week 24 curves for placebo patients.

Fig. 2 Cumulative Percent Weight At Baseline and Week 24 by Treatment



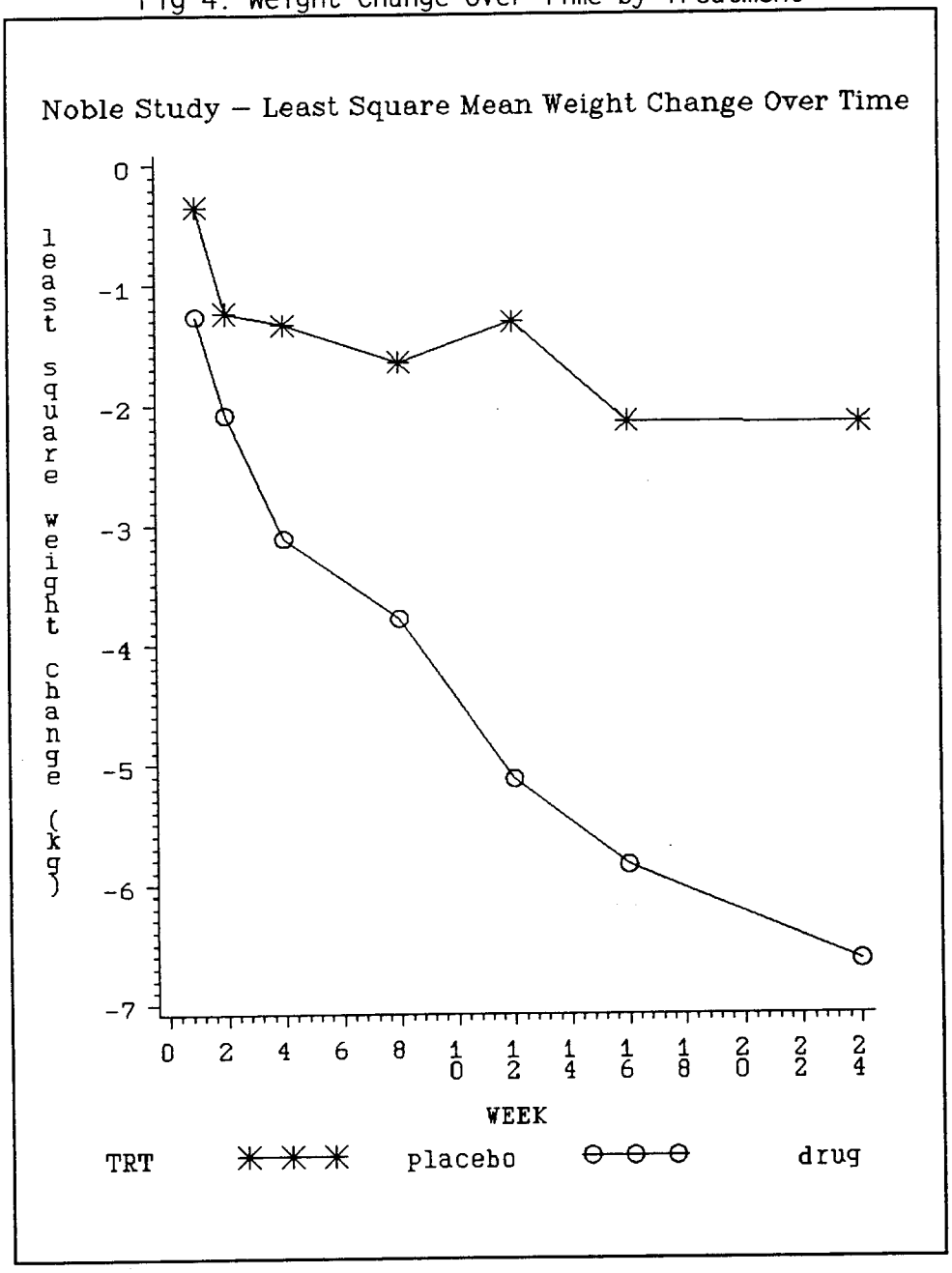
Mean change of weight from baseline by gender is in figure 3.

Fig. 3 Mean Weight Change (kg) Over Time by Gender



The analysis of covariance procedure was applied on the observed cases population. The correlation improved by adding the baseline as covariate in the model for visits 4, 12, 16, 24 ($p<0.2$) on change of weight from baseline. The ANCOVA model included baseline weight (covariate) and drug. Figure 4. is the least square adjusted mean for the change of weight from baseline of the two treatment groups.

Fig 4. Weight Change Over Time by Treatment



The Ancova results are in Table IV. The absolute weight and the change of weight from baseline produce similar p-value with this analysis.

Table IV. Covariance Analysis

Visit		Weight	Change from baseline	% Change from baseline
Week 1	Drug Placebo	94.95(0.26) 95.86(0.27) p=0.02	-1.26 -0.35 p=0.02	1.37(0.28) 0.37(0.28) p=0.02
Week 2	Drug Placebo	93.26(0.28) 94.11(0.28) p=0.04	-2.08 -1.24 p=0.04	2.26(0.31) 1.34(0.31) p=0.04
Week 4	Drug Placebo	92.69(0.39) 94.48(0.40) p<0.01	-3.11 -1.33 p<0.01	3.24(0.40) 1.40(0.41) p<0.01
Week 8	Drug Placebo	92.27(0.63) 94.41(0.61) p=0.02	-3.78 -1.65 p=0.02	4.07(0.62) 1.75(0.61) p=0.01
Week 12	Drug Placebo	90.87(0.92) 94.68(0.86) p<0.01	-5.12 -1.31 p<0.01	5.55(0.93) 1.30(0.86) p<0.01
Week 16	Drug Placebo	90.05(1.09) 93.75(0.99) p=0.02	-5.84 -2.14 p=0.02	6.29(1.06) 2.11(0.96) p=0.01
Week 24	Drug Placebo	89.25(1.43) 93.73(1.29) p=0.03	-6.64 -2.16 p=0.03	7.01(1.38) 2.09(1.25) p=0.01

The median of the last observation carried forward and observed cases are in Table V.

Table V. Median of LOCF(OC)

Visit		Weight	Change from baseline	% Change from baseline
Week 1	Drug Placebo	89.5 99.5	-1.00 -0.20	1.4 0.2
Week 2	Drug Placebo	88.6 99.5	-2.3 -0.9	2.2 1.1
Week 4	Drug Placebo	87.5(85.0) 99.5(99.5)	-3.0(-3.1) -1.3(-1.1)	3.3(3.3) 1.1(2.3)
Week 8	Drug Placebo	86.5(84.0) 97.7(97.0)	-3.2(-3.6) -1.3(-1.4)	3.9(4.5) 1.1(1.5)
Week 12	Drug Placebo	85.4(84.0) 99.5(96.8)	-3.6(-5.5) -0.9(-1.4)	4.7(6.1) 1.1(1.4)
Week 16	Drug Placebo	84.1(79.8) 95.4(95.4)	-5.5(-6.0) -0.9(-0.9)	4.7(7.5) 0.9(0.9)
Week 24	Drug Placebo	80.9(75.9) 96.1(96.1)	-4.4(-5.9) -1.3(-1.4)	4.5(6.7) 1.1(1.2)

With the last observation carried forward, the repeated measure analysis of weight changes from baseline of week 1 to week 24 showed a significant treatment effect for dexfenfluramine over placebo with a p-value of 0.014.

A "clinical significant" approach was applied to the data with 5% or more sustained weight loss after week 4 visit until week 24 visit as a success (See Dr. Lutwak's Interoffice Memorandum 1/6/94). Also, in "The Role of Drug Therapy in Obesity" (Drug Therapy, 9/93), "A 10% to 15% weight loss over 12 to 18 months has been shown to produce significant medical benefits." The last visit of the study was at week 24 therefore, the 10% to 15% weight loss over 12 to 18 months was inapplicable to this study.

From the last observation carried forward data, only 3 patients in drug group and none in placebo had a more than 5% weight loss from week 4 to week 24. From week 8 to week 24 the numbers are 2/27 (7.4%) in placebo and 9/28 (32.1%) in the drug group. P-value from chi-square test was 0.022. The chi-square analysis of observed cases was valid from week 12 on and the p-value was 0.075. For the last observation carried forward the week 12 to week 24 p value was 0.01.

II. Study No. P 003 (IP92-003)

This was a multicenter, parallel, randomized, double-blind, placebo-controlled trial in obese outpatients. Treatment groups of this dose-response study were active drug, 5 mg, 15 mg, 30 mg and placebo. The study consisted of an initial run-in period to determine patient eligibility which included assessment of patient compliance, a 12-week treatment phase and a four-week post-treatment follow-up period.

This U.S. dose-response study was requested by the Agency. The primary objective of this study was to determine which of three dose levels of dexfenfluramine best reduces body weight and produces the fewest adverse events in exogenous obese patients over a 12-week period in combination with a gender- and body weight- specific reduction in caloric intake.

Study Design

This multicenter study was a randomized, double-blind, placebo-controlled parallel trial. Patients were randomized after a 2-week placebo run-in phase to one of the four treatments: placebo, dexfenfluramine 10 mg (5 mg BID), dexfenfluramine 30 mg (15 mg BID), or dexfenfluramine 60 mg (30 mg BID). The 12-week treatment phase was followed by a 4-week post treatment phase.

Patients included were outpatients male or female 18-65 years of age with obesity not of endocrine origin. The body weight was between 120% and 180% of their ideal body weight. Patients were psychologically healthy as defined by DSM-IIIR criteria and physically healthy.

Schedule of Time

1. Placebo Run-in Phase (Week -2 to Baseline) to determine patient eligibility and assessment of dosing compliance.

2. Baseline Phase is considered the day which the first dose (evening) was given.

3. Treatment Phase (week 1 to week 12)
The daily bid dosing of either 0, 10, 30, 60 mg of dexfenfluramine hydrochloride was given in the morning and evening with the meal. Clinic visits were at weeks 1, 2, 4, 8, and 12.

4. Post-Treatment Phase (Weeks 13-16)
After last dose, patients returned for 4 weekly visits. The presence of short-term withdrawal effects were closely monitored at week 13 and week 14 visits.

The protocol plan was to randomize up to 76 obese outpatients (minimum of 28 outpatients) at each of the six study sites.

Patients were instructed to adhere to a calorically-restricted diet. These instructions were reinforced via dietary information and counseling provided at the beginning and throughout the study.

The effectiveness of the various dose levels of dexfenfluramine as an adjunct to reduced caloric intake was assessed by change from baseline in body weight. A food preference/appetite questionnaire was administered at weeks 0, 4, 8, 12, 14, and 16.

Patient Disposition

A total of 339 patients were randomized with 85 to placebo, 85 to 10 mg., 82 to 30 mg and 87 to 60 mg of dexfenfluramine. Seventeen patients withdrew at Week 1 and 96 withdrew after Week 1. A total of 225 patients completed the treatment phase of the study and 204 patients completed the post-treatment phase. The disposition of patients is given in Table VI.

Table VI. Patient Disposition

Patient Disposition	Placebo	10 mg	30 mg	60 mg	Total
Randomized	85	85	82	87	339
Week 1 Dropout	3	1	3	10	17
Evaluable for Efficacy	82	84	79	77	322
Dropout After Week 1	27	24	22	23	96
Completed Active Treatment	55(65%)	59(69%)	57(70%)	54(62%)	225(66%)
Completed Post-Treatment	48(56%)	53(62%)	53(65%)	50(57%)	204(60%)

Demographics

The majority of randomized patients were female (86%) and white (89%) with a mean age of 42.7 years. All patients were at least 108.9% of ideal body weight at baseline.

Deviations from Protocol

Patient No. 1027 who received 10 mg drug was 67 years old outside the protocol eligible age range of 18 years to 65 years, inclusive. The patient received medication for 22 days and was withdrawn from the study at the Week 4 visit by the sponsor because of the protocol deviation.

Patient No. 2065 received 60 mg drug for 16 days and was withdrawn from the study because of pregnancy. Patient No. 7011 in the 60 mg drug group was concerned that she might be pregnant and left the study after taking study medication for two days.

There were 67 patients in violation of protocol for taking disallowed concomitant medication. Nine patients had positive urine drug screen for disqualifying drugs (emphetamines, barbiturates, benzodiazepines, cocaine, hallucinogens, morphine, THC, and alcohol).

Thirty patients were less than 75% compliance to study medication. The protocol specified an entry criterion of 120% to 180% ideal body weight which was defined by the 1983 Metropolitan Life Insurance Company height and weight tables, adjusted for frame size of small, medium, or large. This entry criterion was verified at the study site by the site monitor. Because body frame was not recorded in the case report form there were 44 patients whose entry weight were not eligible. The sponsor viewed it as a reflection of difference in body frame instead a violation of protocol.

Data Analysis

The Sponsor's Analysis

Analysis of variance was performed on the following efficacy variables:

1. Weight
2. Weight loss as a percent of initial overweight
3. Weight loss as a percent of initial weight
4. Change in weight from baseline

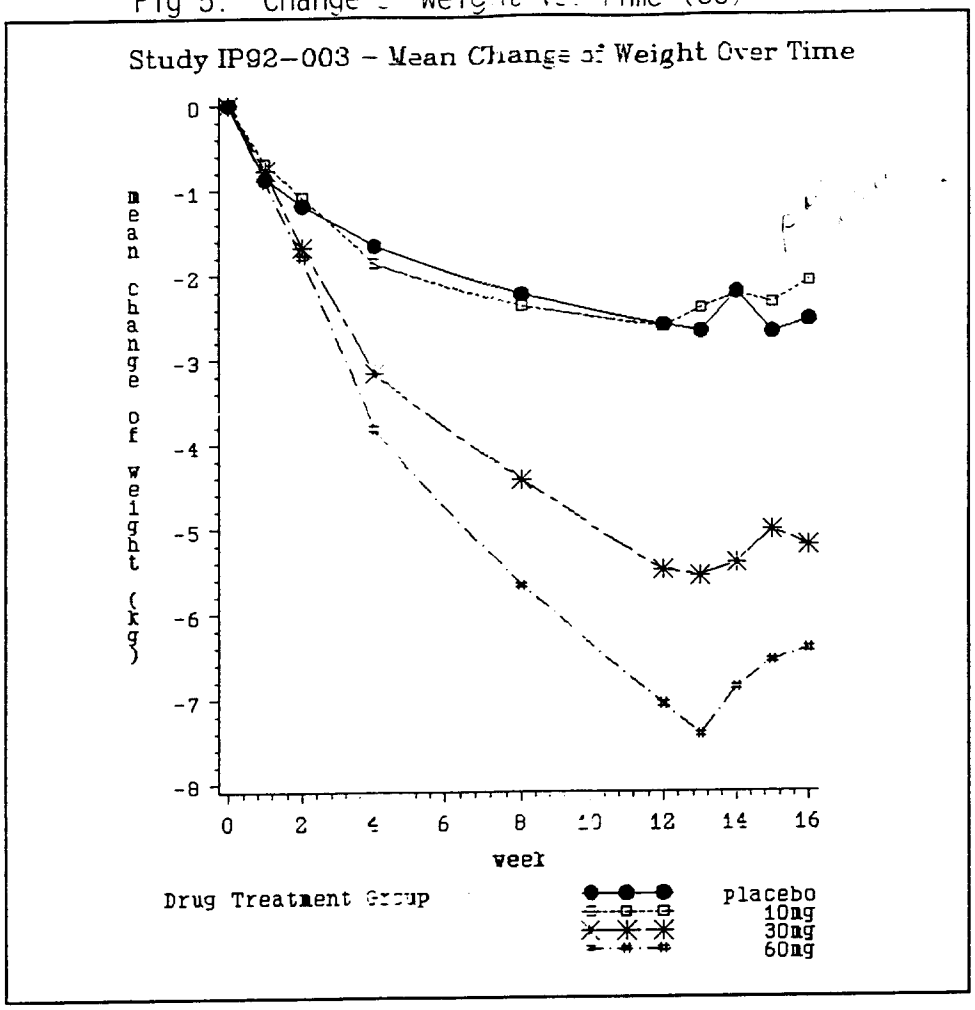
Table VII. Patient Weight by Visit (Observed Cases)

Visit	Treatment N	Weight in Kg	Change from baseline	% Change from baseline
Baseline	Placebo 82 10mg 83 30mg 77 60mg 76	95.8(16.8) 92.9(14.7) 93.0(15.0) 92.6(14.5)p=0.49		
Week 1	Placebo 81 10mg 83 30mg 77 60mg 76	94.5(16.6) 92.3(14.8) 92.2(14.6) 91.7(14.3) p=0.56	-0.9(1.1) -0.7(1.3) -0.8(1.3) -0.9(1.4) p=0.54	0.9(1.2) 0.8(1.5) 0.8(1.3) 1.0(1.4) p=0.63
Week 2	Placebo 77 10mg 77 30mg 70 60mg 71	93.5(16.6) 92.0(14.5) 90.7(14.9) 91.0(14.4) p=0.47	-1.2(1.5) -1.1(1.3) -1.7(1.5) -1.8(1.6) p=0.01	1.3(1.7) 1.2(1.4) 1.8(1.5) 1.9(1.7) p=0.02
Week 4	Placebo 72 10mg 73 30mg 66 60mg 64	93.7(16.7) 91.1(14.3) 89.8(15.0) 89.5(14.7) p=0.15	-1.7(1.7) -1.9(2.1) -3.2(2.0) -3.8(2.1) p<0.01	1.8(1.9) 2.0(2.2) 3.4(2.0) 4.1(2.0) p<0.01
Week 8	Placebo 62 10mg 66 30mg 62 60mg 57	91.5(16.3) 89.5(14.6) 88.3(15.0) 86.8(14.8) p=0.35	-2.3(2.5) -2.4(2.6) -4.4(2.9) -5.7(3.3) p<0.01	2.5(2.7) 2.6(2.9) 4.8(3.1) 6.1(3.2) p<0.01
Week 12	Placebo 55 10mg 60 30mg 57 60mg 54	92.0(16.3) 88.7(14.5) 87.0(15.3) 85.2(15.1) p=0.21	-2.6(3.3) -2.6(3.3) -5.5(3.6) -7.1(4.4) p<0.01	2.8(3.5) 2.9(3.8) 6.0(3.9) 7.6(4.2) p<0.01
Post-treatment follow-up				
Week 13	Placebo 45 10mg 53 30mg 55 60mg 48	92.2(15.4) 89.0(15.0) 87.1(15.5) 84.2(12.7) p=0.11	-2.7(3.5) -2.4(3.7) -5.6(4.0) -7.4(4.1) p<0.01	2.8(3.9) 2.6(4.1) 6.1(4.3) 8.0(3.9) p<0.01
Week 14	Placebo 47 10mg 53 30mg 55 60mg 48	92.3(15.6) 88.5(14.8) 88.0(15.8) 85.7(16.4) p=0.80	-2.2(3.6) -2.2(3.6) -5.4(4.2) -6.9(4.7) p<0.01	2.4(4.0) 2.5(4.1) 5.9(4.3) 7.4(4.6) p<0.01
Week 15	Placebo 44 10mg 51 30mg 49 60mg 47	92.6(15.9) 88.5(14.9) 87.8(16.2) 84.2(12.5) p=0.10	-2.7(3.8) -2.4(3.6) -5.0(4.9) -6.6(4.6) p<0.01	2.8(4.2) 2.5(4.1) 5.6(5.2) 7.1(4.6) p<0.01
Week 16	Placebo 48 10mg 55 30mg 53 60mg 50	91.6(16.0) 89.4(15.1) 87.8(16.2) 86.3(16.0) p=0.70	-2.6(3.9) -2.1(3.9) -5.2(4.9) -6.4(5.2) p<0.01	2.7(4.3) 2.3(4.5) 5.7(5.1) 6.9(5.1) p<0.01

No statistically significant differences were found among the four treatment groups with respect to the actual weight measurements at each of the scheduled visits for patients continuing in the study. For the endpoint analysis, using the last value carried forward, however, a statistically significant difference in body weight was observed among the four treatment groups($p<=0.05$).

The mean change of weight over time for observed cases is in Fig 5.

Fig 5. Change of Weight vs. Time (OC)



After week 12, it was the post-treatment phase. Patients were to continue on their prescribed diets during that period.

Reviewer's Analysis

The placebo and 30 mg drug groups are in the analysis for observed cases.

The week 1 (week 12) number of patients in each center and treatment group is in Table VIII.

Table VIII. Number of Patients at Week 1 and (Week 12)

Center	Placebo	10 mg	30 mg	60 mg	Total
1	18(10)	19(17)	18(13)	16(12)	71(52)
2	16(14)	16(12)	16(13)	16(11)	64(50)
3	10(7)	11(5)	10(9)	10(4)	41(25)
4	18(12)	19(13)	15(13)	17(12)	69(50)
5	10(7)	10(7)	9(4)	10(8)	39(26)
6	9(5)	8(6)	9(5)	7(7)	33(23)
Total	81(55)	83(60)	77(57)	76(54)	317(226)

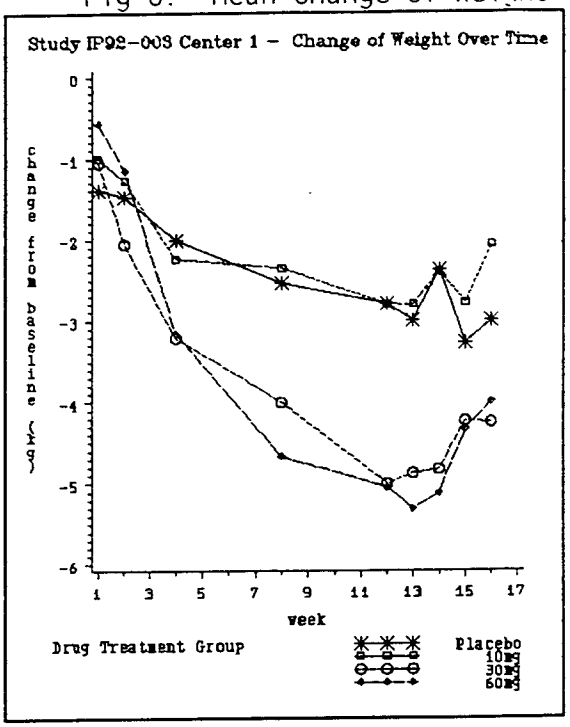
The analysis of variance results on change of weight from baseline are in Table IX with center drug and drug by center interaction in the model. The least square adjusted mean and standard error are displayed by center and drug for each visit.

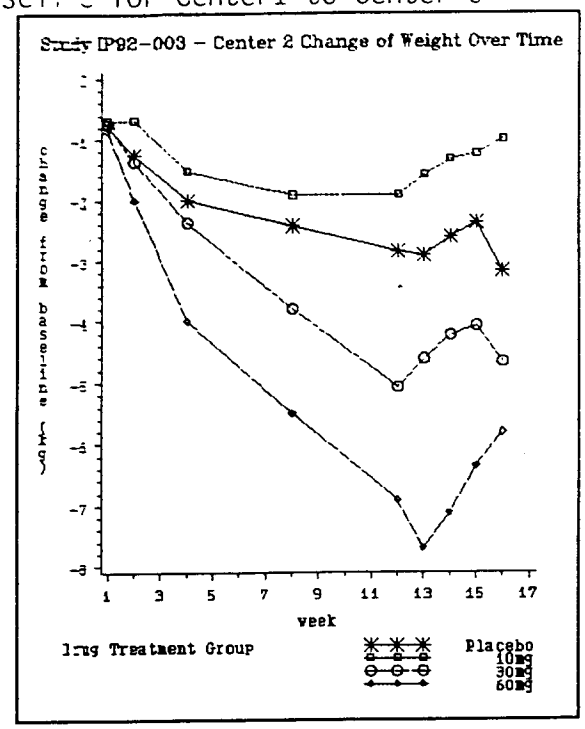
Table IX Absolute Weight Change from Baseline

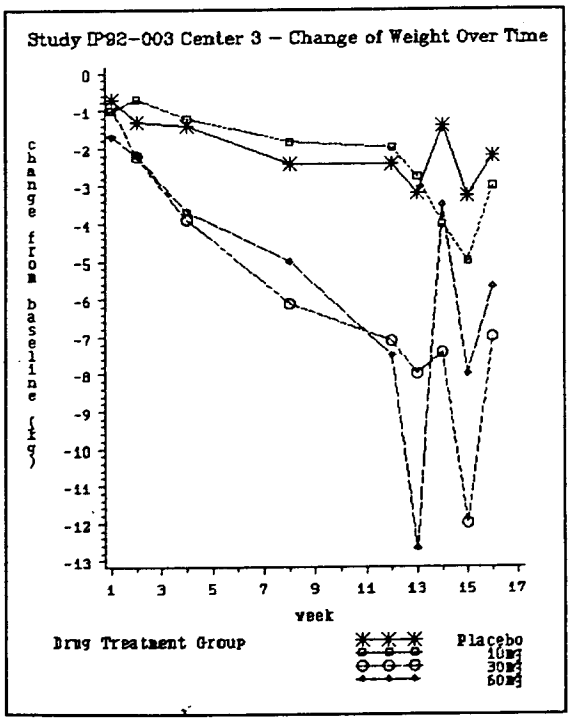
Week	Treatment	Center 1	Center 2	Center 3	Center 4	Center 5	Center 6	p-value
1	Placebo	-1.39(0.27)	-0.81(0.29)	-0.70(0.37)	-0.61(0.27)	-1.16(0.37)	-0.33(0.39)	0.895
	30 mg	-1.06(0.27)	-0.75(0.29)	-0.90(0.37)	+0.06(0.30)	-1.32(0.39)	-0.89(0.39)	
2	Placebo	-1.47(0.36)	-1.25(0.37)	-1.30(0.47)	-1.09(0.36)	-1.46(0.50)	-0.25(0.53)	0.017
	30 mg	-2.06(0.36)	-1.38(0.37)	-2.22(0.50)	-0.96(0.39)	-2.33(0.61)	-1.71(0.56)	
4	Placebo	-2.00(0.47)	-2.00(0.48)	-1.40(0.57)	-0.94(0.44)	-2.91(0.60)	-0.86(0.68)	0.0001
	30 mg	-3.21(0.48)	-2.38(0.45)	-3.89(0.60)	-2.93(0.48)	-4.05(0.74)	-3.57(0.68)	
8	Placebo	-2.54(0.74)	-2.43(0.71)	-2.43(1.01)	-1.14(0.71)	-3.96(0.94)	-1.33(1.08)	0.0001
	30 mg	-4.00(0.71)	-3.80(0.69)	-6.11(0.89)	-3.77(0.74)	-4.56(1.33)	-5.57(1.01)	
12	Placebo	-2.80(1.07)	-2.86(0.91)	-2.43(1.28)	-0.39(0.98)	-5.53(1.28)	-3.00(1.28)	0.0001
	30 mg	-5.00(0.94)	-5.08(0.94)	-7.11(1.13)	-5.00(0.94)	-4.61(1.69)	-7.00(1.51)	

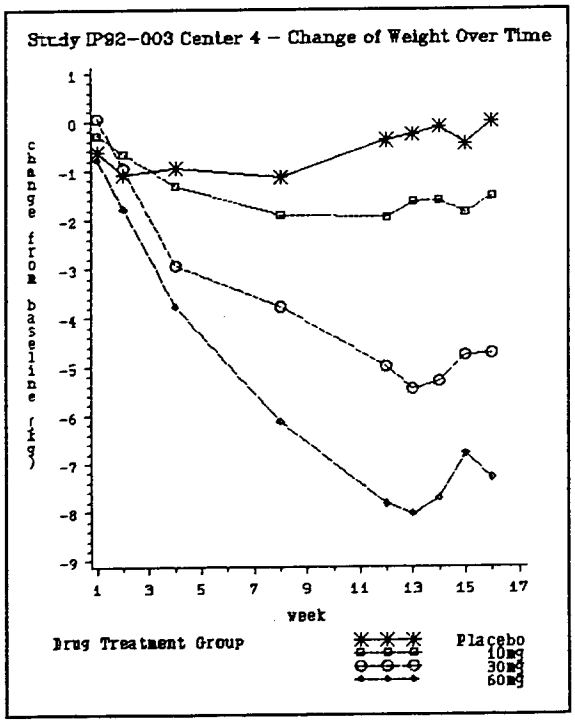
The drug and center interactions are not significant ($p>0.2$).
The weight loss by center over time is in the following figures.

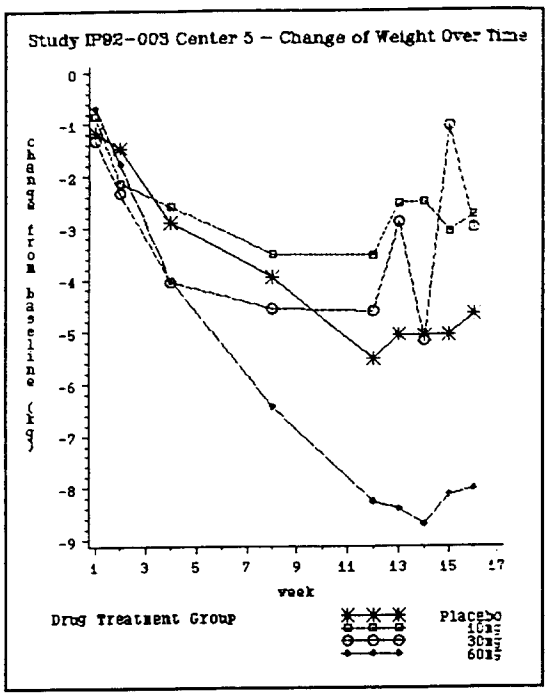
Fig 6. Mean Change of Weight from Baseline for Center1 to Center 6

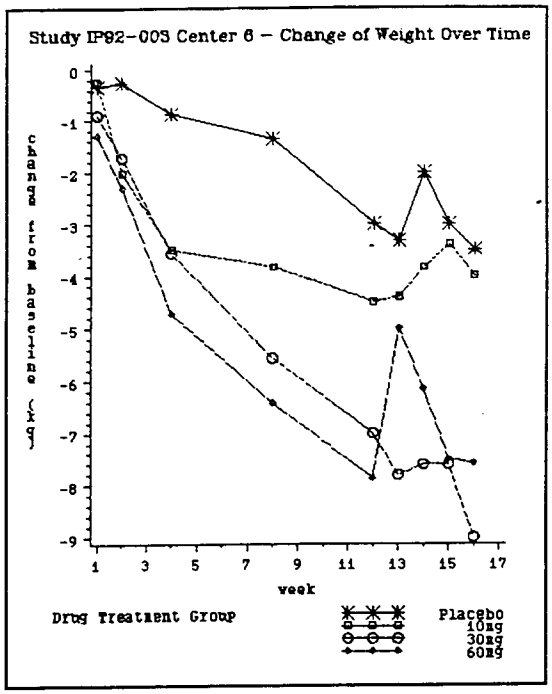






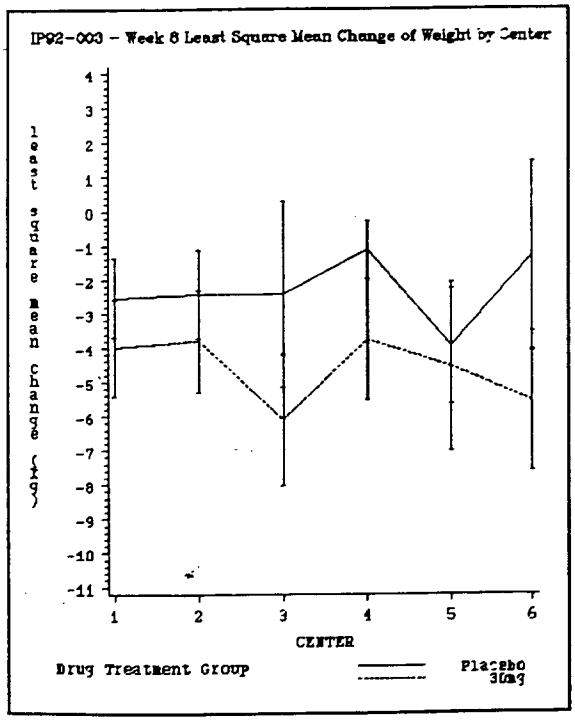


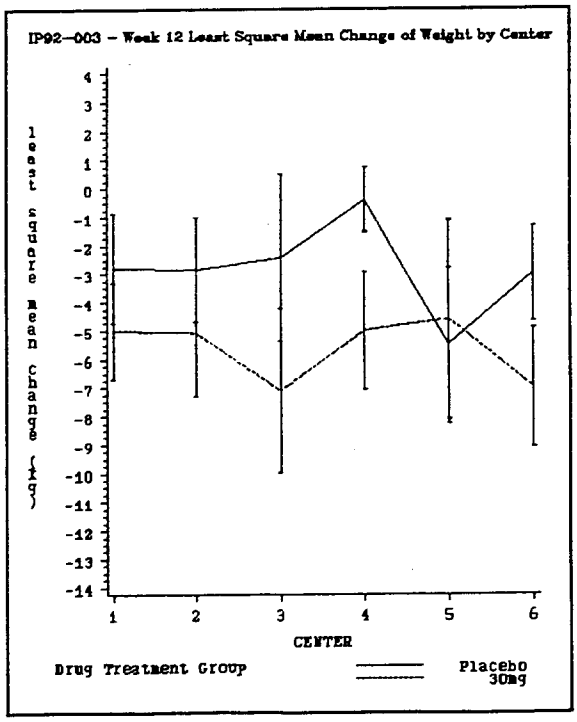




For the 30mg group and placebo comparison, the least square mean change of weight with the ANOVA model of drug, center and drug by center interaction is in figures 4 and 5 for weeks 8 and week 12, respectively. The vertical bars are the standard error bars of the mean derived from the analysis.

Fig 7. Least Square Adjusted Mean Change of Weight by Center





The sustained 5% more weight loss during study was examined. Comparing 30 mg dexfenfluramine to placebo, the observed case results are p=0.59 for week 4 to week 16, p=0.013 from week 8 to week 16, p=0.001 for week 12 to week 16, and p=0.001 for week 13 to week 16. The last observation carried forward results are p=0.039, p=0.001, p<0.001, p<0.001, respectively. The homogeneity test of odds ratios among centers was also significant, however, suggesting that results differed among centers.

III. Index Study

This is an international multicenter study with long-term administration of dexfenfluramine in obese patients.

Summary of Study Protocol:

The protocol called for 450 patients with 225 receiving 30 mg dexfenfluramine (one capsule 15mg twice a day) and the other 225 receiving placebo capsules for one year. Dietary advice will be given to all patients. The number of patients from each center should not be less than 20 and should not exceed 40 and the inclusion period should not exceed 6 months. Efficacy assessment are at 1, 2, 4, 6, 8, 10 and 12 months. The study includes patients over 18 years of age with a body weight greater or equal to 120% of their ideal weight. One of the exclusion criteria is weight loss greater than 3 kg during the previous 3 month period.

For randomization, in each center there are two separate randomized study medication boxes: one box, stratum W, to allocate the treatment to patients with body weight equal or greater than 135% of their ideal weight, one box, stratum Z, to allocate treatment to patients with body weight less than 135% but greater than 120% of their ideal weight. For a given center, the randomization list was the same for both Z and W subgroups. The randomization was done in blocks of six. No sample size calculations was presented in the protocol.

The primary efficacy variable is the absolute change in weight from baseline measured in kilograms.

Results

One thousand and forty-seven patients enrolled in the study with 520 randomized with dexfenfluramine treatment and 527 in the placebo treatment. Two patients randomized to dexfenfluramine did not receive study medication were excluded from efficacy population. Also excluded are 17 dexfenfluramine patients and 21 placebo patients who took baseline assessments after taking study medication.

Patient disposition for efficacy evaluation is in the following table.

Table X. Index Study - Patient Disposition

Patient Disposition	Dexfenfluramine	Placebo	Total
Randomized	520	527	1047
Evaluable at Month 1	469(91%)	472(90%)	941
Month 2	443(85%)	430(82%)	873
Month 4	401(77%)	377(72%)	778
Month 6	366(70%)	336(64%)	702
Month 8	336(65%)	306(58%)	642
Month 10	312(60%)	280(53%)	592
Month 12	298(57%)	262(50%)	560

The selected patient characteristics of the two treatment for the two stratum are in Table XI.

Table XI. Index Study - Patient Demographics

	Treatment Group					
	Drug	Placebo	Stratum W		Stratum Z	
			Drug	Placebo	Drug	Placebo
N	518	527	108	104	410	423
Mean Baseline Weight (kg)(SD)	96.5 (19.6)	97.2 (18.6)	77.9 (7.2)	78.0 (7.4)	101.5 (18.8)	102.3 (17.4)
Mean Body Mass Index (kg/m^2) (SD)	35.6 (5.9)	35.8 (6.0)	29.5 (1.6)	29.3 (1.9)	37.3 (5.6)	37.5 (5.6)
Mean Age (years) (SD)	40.3 (12.5)	41.6 (12.5)	40.4 (13.2)	45.0 (12.9)	40.3 (12.4)	40.8 (12.3)
Gender n(%)						
Male	102 (19.7%)	108 (20.5%)	15 (13.9%)	16 (15.4%)	87 (21.2%)	92 (21.7%)
Female	416 (80.3%)	419 (79.5%)	93 (86.1%)	88 (84.6%)	323 (78.8%)	331 (78.3%)

There were no statistically significant differences between the two treatment groups with respect to the tabled characteristics.

Deviation from protocol

Table XII lists number of patients with protocol deviations. All patients with protocol deviations are included in the efficacy analyses.

Table XII. Index Study - Patients with Protocol Deviation

Deviation	Drug	Placebo
Obesity<120%	1	1
Age<18	0	1
Weight Loss>3kg	3	1
Present Weight<85% maximal weight ever	0	1
Obesity Origin endocrine	1	4
Other Inclusion/ Exclusion Criteria	6	2
Stratification Incorrect	6	8
Total	17	18

Efficacy Results

The mean weight changes from baseline of patients continuing in study (observed cases. OC) and the last observation carried forward (LOCF) results are in Table XIII.

Table XIII. Index Study - Absolute Weight Change from Baseline

Timepoint (Week)	Dexfenfluramine		Placebo		p-value OC&LOCF
	OC	LOCF	OC	LOCF	
Screen (-9)	96.7(19.7) n=468		97.2(18.7) n=472		
Baseline (0)	96.8(19.6) n=469		97.4(18.7) n=472		0.65
Month 1 (4)	-4.1(3.0) n=463		-2.9(2.7) n=466		<=0.0001
Month 2 (8)	-6.3(4.2) n=440	-6.1(4.2) n=463	-4.5(4.2) n=424	-4.3(4.2) n=464	<=0.0001
Month 4 (12)	-8.8(5.7) n=396	-8.0(5.8) n=461	-6.3(5.9) n=375	-5.5(5.8) n=465	<=0.0001
Month 6 (24)	-9.7(6.3) n=359	-8.7(6.4) n=460	-6.9(6.8) n=333	-5.8(6.5) n=467	<=0.0001
Month 8 (32)	-9.8(6.6) n=326	-8.5(6.6) n=456	-7.1(7.3) n=297	-5.8(6.9) n=462	<=0.0001
Month 10 (40)	-9.7(7.1) n=309	-8.4(6.9) n=461	-7.3(7.7) n=276	-5.7(7.0) n=464	<=0.0001
Month 12 (48)	-9.6(7.7) n=297	-8.3(7.3) n=463	-6.9(8.0) n=262	-5.4(7.1) n=467	<=0.0001
2-Month Follow-up(56)	-7.9(8.2) n=278		-6.1(8.2) n=239		

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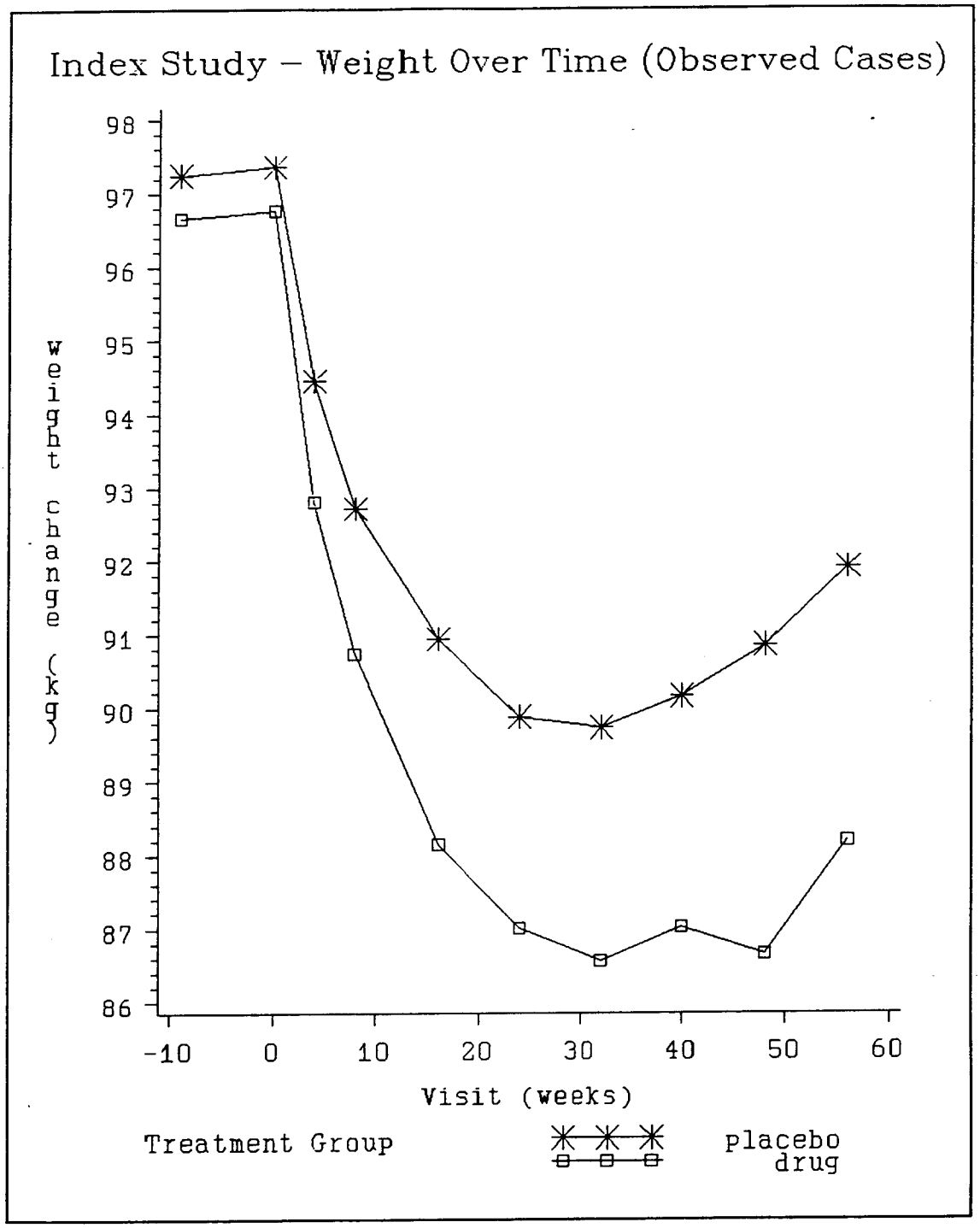
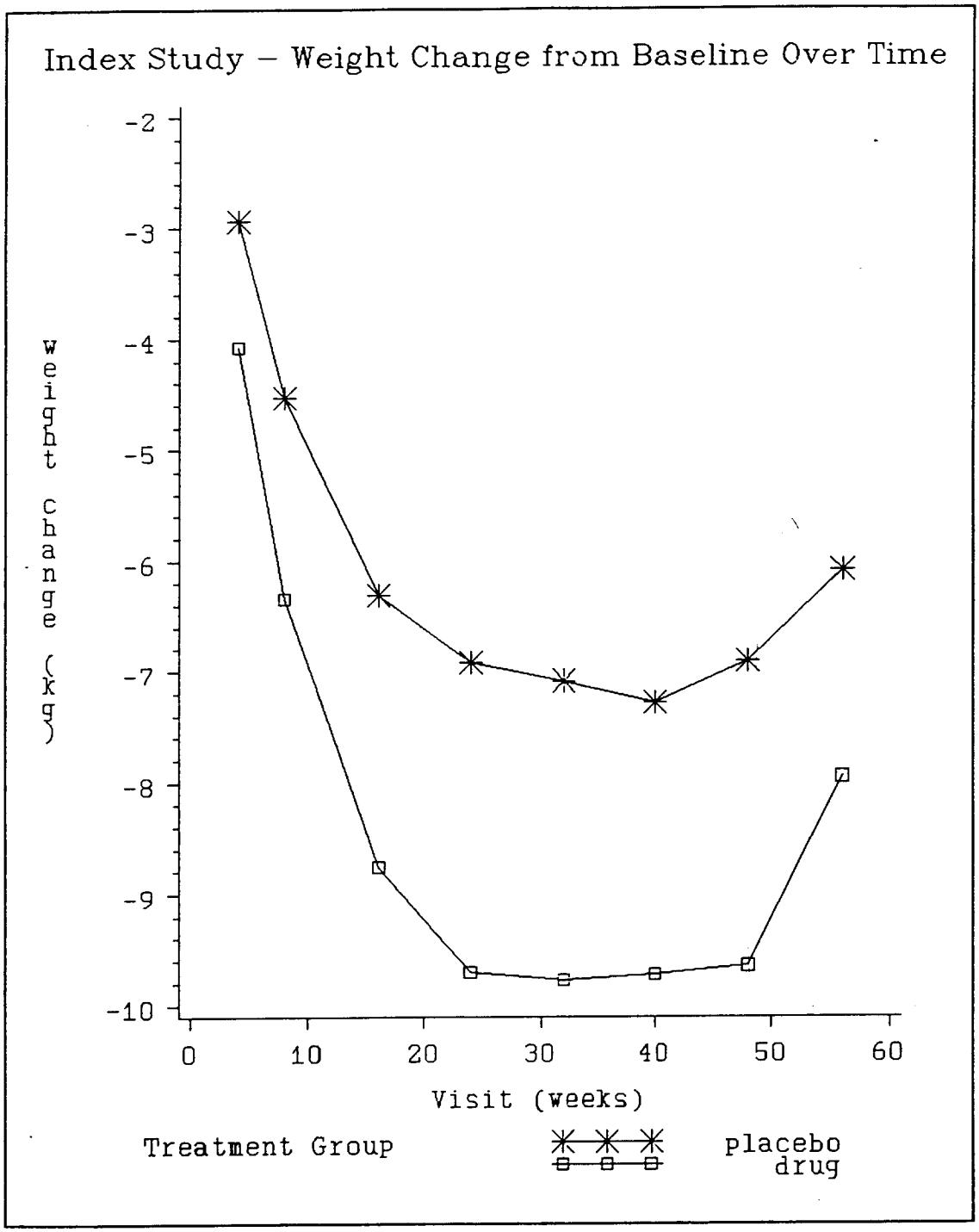
For the observed cases, the mean weight of patients over time for placebo group and drug group is in Fig. 14.

Fig. 14. Mean Weight from Screening (-9) to 2-Month (56) Follow-up



The change of weight from baseline is in Fig. 15 for the observed cases.

Fig. 15. Mean Weight Change from Baseline to 2-Month Follow-up



Week 56 is the 2-month follow-up visit after the 12-month treatment.

The least square adjusted mean weight change from baseline at week 48 (end of study) and week 56 (2-month follow-up) of observed cases are in Fig. 16 and Fig. 17, respectively.

Fig. 16. Week 48 Mean Change

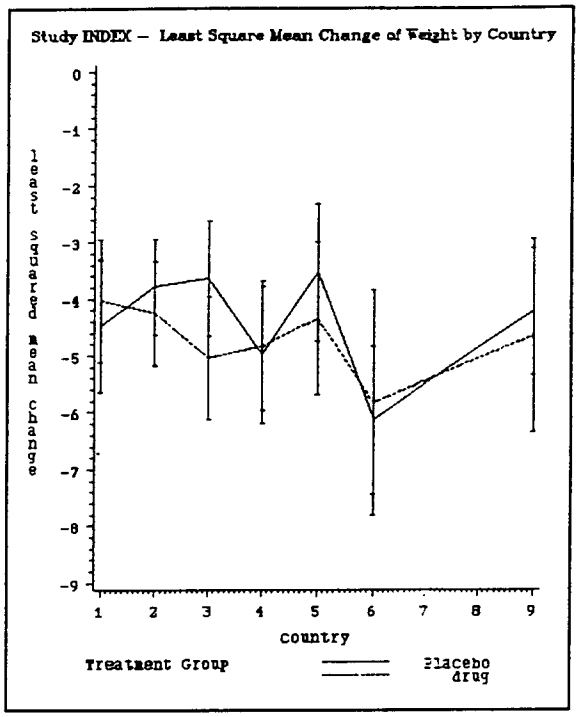
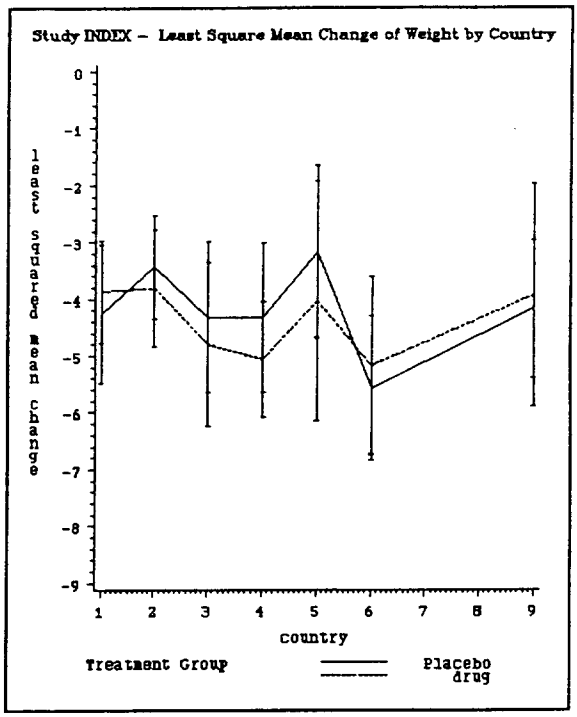


Fig. 17. Week 56 Mean Change



Country: 1=France; 2=UK; 3=Germany; 4=Virtual Country (Switzerland, Denmark, The Netherlands); 5=Austria; 6=Belgium; 9=Italy

Conclusion:

There were statistically significant differences between 30 mg dexfenfluramine and placebo. The weight loss was 8.5 (C.I. 8.0-9.1) for dexfenfluramine versus 5.3 (C.I. 4.7-5.8) for placebo at Month 6 of the Index study. It is for the clinicians to decide whether this is clinically meaningful.

IV. Other controlled trials:

It is not clear why the other controlled trials were not considered "well-controlled" by the sponsor. One question is whether the other trials supported the sponsor's case, or were considered "not well-controlled" because of less favorable results. Most of these trials do seem, however, to support the efficacy of dexfenfluramine. Table XIV below gives some basic descriptive information on these trials.

Table XIV. Summary of Controlled Clinical Trials

Study No. Location (No. of Centers)	Population	Duration (Month)	Treatment Group (#randomized/ completed)	Baseline Weight	End-of-Study Weight Change (LOCF)
Noble US(1)	Partially Successful Obese Dieters	6	Drug 30/19 Placebo 30/23 Absolute Diff p-value(parametric) p-value(non-parametric)	93.1 99.4 0.6 NS	-4.9(n=28) -2.3(n=27) 2.6 0.1 0.0062
IP92-003 US(7)	Obese Patients	3	Drug 82/57 Placebo 85/55 Absolute Diff p-value	93.0 95.8 2.8 NS	-4.6(n=77) -2.0(n=80) 2.6 0.0001
Index 9 European Countries(24)	Patients with simple Obesity	12	Drug 520/311 Placebo 527/280 Absolute Diff p-value	96.8 97.4 0.6 NS	-8.2(n=463) -4.8(n=467) 3.4 0.0001
MIT-124 US(1)	Obese Carbohydrate Cravers and Obese Non-Cravers	3	Drug 40/32 Placebo 40/38 Ablolute Diff p-value	96.2 99.9 3.7 NS	-2.4(n=35) +1.3(n=37) 3.7 0.0001
MIT-296 US(1)	Obese Female Carbohydrate Cravers	3	Drug 28/22 Placebo 29/25 Ablolute Diff p-value	85.7 88.2 2.5 NS	-5.5(n=27) -2.9(n=28) 2.6 0.018
Van Itallie(1)	Obese Patients	3	Drug 57/41 Placebo 29/14 Absolute Diff p-value	93.2 94.9 1.7 NS	-4.0(n=51) -2.1(n=24) 1.9 0.0407
C 5614 34 012 Italy (1)	Patients with Simple Obesity	3	Drug 19/10 Placebo 17/12 Absolute Diff p-value	86.4 86.5 0.1 NS	-4.4(n=16) -0.5(n=14) 3.9 0.0072
C 5614 34 013 Italy (1)	Patients with Simple Obesity	3	Drug 20/18 Placebo 20/20 Absolute Diff p-value	81.1 84.9 3.8 NS	-8.7(n=20) -6.0(n=20) 2.7 0.0272

Study No. Location (No. of Centers)	Population	Duration (Month)	Treatment Group (#randomized/ completed)	Baseline Weight	End-of-Study Weight Change (LOCF)
C 5614 34 014 Italy (1)	Patients with Simple Obesity	3	Drug 18/12 Placebo 18/14 Absolute Diff p-value	79.2 84.5 5.3 NS	-9.1(n=12) -3.3(n=14) 5.8 0.0009
C 5614 34 016 Italy (1)	Simple Obesity	3	Drug 14/14 Placebo 14/14 Absolute Diff p-value	85.5 79.7 5.8 NS	-9.0(n=14) -6.1(n=14) 2.9 0.0441
C 5614 34 017 Italy (1)	Simple Obesity	3	Drug 15/12 Placebo 15/10 Absolute Diff p-value	86.0 86.5 0.5 NS	-6.9(n=14) -5.7(n=14) 1.2 NS
C 5614 34 018 Italy (1)	Simple Obesity	3	Drug 23/22 Placebo 25/23 Absolute Diff p-value	88.1 90.5 2.4 NS	-8.6(n=23) -2.9(n=24) 5.7 0.0001
C 5614 34 001 France (1)	Simple Obesity	3	Drug 27/22 Placebo 27/20 Absolute Diff p-value	87.3 78.2 9.1 0.0348	-9.6(n=27) -5.1(n=26) 4.5 0.0001
C 5614 34 010 UK (1)	Simple Obesity	3	Drug 41/34 Placebo 34/28 Absolute Diff p-value	82.0 77.9 4.1 NS	-4.2(n=36) -1.9(n=32) 2.3 0.0016
C 5614 34 002 UK(1)	Patients with Refractory Obesity	3	Drug 26/18 Placebo 24/22 Absolute Diff p-value	81.7 81.9 0.2 NS	-3.9(25) -1.4(24) 2.5 0.0267
C 5614 34 003 UK (1)	Patients with Refractory Obesity	3	Drug 19/17 Placebo 20/19 Absolute Diff p-value	91.5 88.5 3.0 NS	-2.5(n=19) +1.6(n=19) 4.1 0.0002

One additional study, Study IP92-005, is an US multicenter study with 10 investigators. Study length is 18 weeks with 2-week placebo run-in, 12 week treatment and 4-week follow-up. The study has been completed and in process of analysis.

V. Overall Conclusions:

Dexfenfluramine 10 mg was not effective for weight loss compared to placebo in the one study reviewed. Sufficient statistical evidence has been shown from the 3 studies reviewed that 30 mg is significantly better than placebo.

Lee-Ping Pian

Lee-Ping Pian Ph.D.
Mathematical Statistician

Concur: Dr. Nevius 5-5-94

Dr. Dubey 5-6-94

cc: Orig. NDA 20-323
HFD-510
HFD-510/Dr. Sobel
HFD-510/Dr. Troendle
HFD-510/Dr. Lutwak
HFD-510/Dr. Stockbridge
HFD-713/Dr. Dubey [File:DRU 1.3.2]
HFD-344/Dr. Lisook
HFD-713/Group 2 File
HFD-713/Dr. Pian
Chron.

Pian/x4710/wp/5/5/94

This review contains 31 pages and 17 figures

NDA 20-344

FEB 17 1995

Interneuron Pharmaceuticals Incorporated
Attn: Bobby Sandage, Jr., Ph.D.
Senior Vice President, Research and Development
One Ledgemont Center
99 Hayden Avenue, Suite 340
Lexington, MA 02137

Dear Dr. Sandage:

Please refer to your May 21, 1993, New Drug Application submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Dexfenfluramine Capsules (15 mg).

We acknowledge receipt of your amendments dated October 27 and December 14, 1993, and January 11, February 23, March 7, April 28, and May 3, 1994.

We have completed our review of this application and find that the information presented is inadequate, and the application is not approvable under section 505(d) of the Act and 21 CFR 314.125(b) of FDA's implementing regulations. The deficiencies may be summarized as follows:

I. Clinical

A. The application does not contain adequate safety data to define the risk of developing pulmonary hypertension. The prospective case-controlled epidemiologic study, which has been conducted in several countries where the drug has been approved for use, has not been submitted to the NDA.

B. Neurotoxicity was observed in animals (mice, rats, and monkeys). The potential for neurotoxicity in humans has not been adequately evaluated to assess the drug product's risks relative to its benefits.

II. Chemistry

A. Drug Substance

1. The identification tests for raw materials should be highly specific. Methods such as more than one test, should be performed to ensure that these substances are unequivocally identified.

2. The bulk drug substance must be tested for

3. The type used in the bulk drug substance storage container should be specified and its suitability justified.

4. Dexfenfluramine hydrochloride

A validated analytical assay method that is specific should be utilized and incorporated into the specifications.

5. be included as part of the drug substance specifications.

B. Drug Product

1. The assay method for the dosage form should also be

2. A letter of authorization for the manufacturer of the components of the container/closure system) type 1 DMF is required.

3. Stability studies should include monitoring the degradation products by a quantitative

4. To support the two-year expiration date requested in the NDA, additional stability information is required for drug product stored in the three types of bottles which will be marketed.

5. Draft labels for containers and cartons, and all other packaging, must be submitted.

6. Stability data of the capsule dosage form made with drug substance from the material must be submitted.

C. Letters requesting responses to deficiencies in Drug Master Files and have been sent to their respective holders.

III. Pharmacology

A. A toxicology study in primates is necessary to identify the minimal dose that produces toxicity so that a "no-effect" level can be identified. The serum drug levels in monkeys should be compared with the serum drug levels in humans in order to evaluate the safety margin.

B. The brain drug levels in rats and monkeys should be compared with the brain drug levels in humans using Positron Emission Tomography or a similar technique.

C. The tumor data and p-values should be submitted in tabular form for the rat and mouse carcinogenicity studies. The preferred table format is with the dosage groups (male and female) across the top of the table and the organ and tumor type [designated benign (B) or malignant (M)] shown vertically. The number per group as well as the number examined per group for each organ should be given. These tables should contain analyses, comparing treated to control, and should include trend tests. Any historical supporting data should be submitted in a similar format.

IV. Biopharmaceutics

A. It is reported in the NDA that the dexfenfluramine AUC is significantly greater for females than for males (Study IP92-001, Volume 1.64, pages 39-40). In addition to the reported mean AUC values, statistical analyses including the sample size (n), p-value, and standard deviation, or CV, (with and without body weight adjustment), should be provided to support this conclusion. Similar comparative data should also be provided for d-norfenfluramine.

B. In Study PMH 5614 01 007 (Volume 1.73, page 21), it is stated that:

(a) "A statistically significant reduction in weight was seen after four weeks and for the remainder of the 12-week course of this study in patients who were treated with dexfenfluramine plus diet versus placebo plus diet". (A mean steady state plasma d-fenfluramine concentration of "18.1 ng/mL" was reported for the patients).

(b) "When the patients were grouped according to mean steady state plasma levels (< 10 ng/mL and > 10 ng/mL), patients with levels greater than 10 ng/mL showed a more rapid and prolonged weight loss compared with patients with plasma levels less than 10 ng/mL".

A summary of the statistical comparison, including the mean values, standard deviation (or CV), p-value and number of subjects (n), should be provided to support both conclusions.

C. For the single dose study PMH 5614 01 007, the reported dose-normalized d-fenfluramine and d-norfenfluramine AUC_{0-8} and C_{max} values decrease consistently with increasing d-fenfluramine dose. We consider the duration of sampling (0-8 h post dose) to be inadequate for generating kinetic data to demonstrate dose proportionality of d-fenfluramine ($t_{1/2}$ = 18.1 h) and d-norfenfluramine ($t_{1/2}$ = 32.4 h). Therefore, we do not agree with your conclusion that this study demonstrates that the kinetics of d-fenfluramine and d-norfenfluramine are dose-proportional.

D. The design of Study 6514 01 008 was not adequate to evaluate the effect of

food on the kinetics of d-fenfluramine and d-norfenfluramine. The fasted and fed study treatments were conducted four years apart and, for the fed treatment, the classical FDA food challenge was not used. Also, the effect of food on the kinetics of the active metabolite, d-norfenfluramine, was not assessed. Therefore, a new, well-controlled food effect study is needed.

E. For Study 88 5614 001, only the kinetics of d-fenfluramine were evaluated in the elderly. Since data in published reports indicate that d-norfenfluramine is more potent than d-fenfluramine, an assessment of the kinetics of d-norfenfluramine in the elderly is also needed.

F. For Study IP92-004, Tables I and K appear to show that only data from 20 of the 35 evaluable subjects were used in calculating the two one-sided t-tests (90% confidence intervals) comparing the to-be-marketed, U.S.-made, 15 mg capsule formulation, to be clinically tested, to the French-made 15 mg capsule formulation. The reason(s) for excluding the data for the other 15 subjects from the analyses should be stated.

G. The data demonstrating the accuracy of the analytical method for the reported assay linearity range (with individual concentrations and CV values) should be provided for Studies PMH 6514 003, PMH 5614 OO4, PMH 5614 007, and 88 5614 001. For Studies PMH 5614 01 008 and PMH 5614 009, in which accuracy values were already provided, individual concentrations and CV should be submitted.

H. The data demonstrating between-run precision of the analytical method for the reported assay linearity range should be provided for Studies PMH 6514 003, PMH 5614 OO4, PMH 5614 007, PMH 5614 01 008, PMH 5614 009, and 88 5614 001. The individual concentrations and CV values should be provided.

In addition, we have the following comments and requests for information that should be addressed:

o

1. You attribute the changes in dissolution rate at (accelerated conditions), and occasionally at standard conditions), to the What evidence do you have to reject the possibility that the

2. Any information on the enzymes involved in the metabolism of d-norfenfluramine should be provided.

3. A proprietary name for dexfenfluramine capsules should be submitted to the FDA.

4. In the description section of the package insert, "pharmaceutical class" should be deleted. The established name of the drug product must follow the trade name in the heading, and whenever the trade name first appears on a page or column as described in 21 CFR 201.10 (g)(1).

5. The labeling requires revision according to 21 CFR 201.57 (f) (6). When plasma drug levels are available, human exposure should be expressed in terms of multiples of the AUC observed in preclinical studies. In the absence of plasma drug levels, drug exposure comparisons between preclinical and clinical doses should be based on surface area (mg/m^2) rather than on mg/kg.

   The words "Two additional" should be removed from the sentence regarding the teratogenicity studies.

Within 10 days after this letter, you are required to amend the application, notify us of your intent to file an amendment, or follow one of your other options under 21 CFR 314.120. In the absence of any such action FDA may proceed to withdraw the application. Any amendment should respond to all the deficiencies listed. We will not process a partial reply as a major amendment nor will the review clock be reactivated until all the deficiencies are addressed.

In addition, we must receive satisfactory reports concerning the inspection of the manufacturing facility in Toledo, Spain, and audits of pivotal clinical trials.

Should you have any questions, please contact Dr. Lisa Stockbridge (Consumer Safety Officer) at 301-443-3520.

Sincerely yours,

James Bilstad 2/17/95

James Bilstad, M.D.
Director
Office of Drug Evaluation II
Center for Drug Evaluation and Research

Name	Title	Signature	Date
Enid Galliers	SCSO	Enid Galliers	2-17-95
Leo Lutwak, M.D.	Medical Officer	Leo Lutwak	2-17-95
Gloria Troendle, M.D.	Supervisory Medical Officer	Gloria Troendle	2-17-95
Xavier Ysern, Ph.D.	Chemist	Xavier Ysern	17 FEB 1995
Yuan-Yuan Chiu, Ph.D.	Supervisory Chemist	Yuan-Yuan Chiu	Feb. 17, 1995
David Hertig	Pharmacologist	A Jordan for D Hertig	2/17/95
Alexander Jordan, Ph.D.	Supervisory Pharmacologist	A Jordan	2/17/95
Solomon Sobel, M.D.	Division Director	S Sobel	2/17/95

APPEARS THIS WAY
ON ORIGINAL

cc:
Arch NDA
HFD-510
DISTRICT OFFICE
HFD-713
HFD-500/JBilstad
HFD-426/JHunt/DUdo
HFD-400/JContrera
HFD-510/SSobel/GTroendle/LLutwak/YChiu/XYsern/AJordan/DHertig/EGalliers
HFD-80
HFD-007/MKlein
HFD-510/LStockbridge/8.8.94\N20344NA.000 2-17-95

Concurrences:

NOT APPROVABLE

APPEARS THIS WAY
ON ORIGINAL

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION

APPLICATION TO MARKET A NEW DRUG FOR HUMAN USE OR AN ANTIBIOTIC DRUG FOR HUMAN USE

(Title 21, Code of Federal Regulations, 314)

Form Approved: OMB No. 0910-0001
Expiration Date: April 30, 1994
See OMB Statement on Page 3.

FOR FDA USE ONLY	
DATE RECEIVED	DATE FILED
DIVISION ASSIGNED	NDA/ANDA NO. ASS.

NOTE: No application may be filed unless a completed application form has been received (21 CFR Part 314).

NAME OF APPLICANT	DATE OF SUBMISSION
Interneuron Pharmaceuticals, Inc.	Sept 19 1995
ADDRESS (Number, Street, City, State and Zip Code)	TELEPHONE NO. (Include Area Code)
99 Hayden Avenue, Suite 340 Lexington, MA 02173	617/861-8444
	NEW DRUG OR ANTIBIOTIC APPLICATION NUMBER (If previously issued) 20-344

DRUG PRODUCT

ESTABLISHED NAME (e.g., USP/USAN)	PROPRIETARY NAME (If any)
dexfenfluramine hydrochloride	REDUX™

CODE NAME (If any)	CHEMICAL NAME
S-614 S-5614	(S)-N-ethyl- α -methyl-3-(trifluoromethyl) benzeneethanamine, hydrochloride

DOSAGE FORM	ROUTE OF ADMINISTRATION	STRENGTH(S)
capsule	oral	15mg

PROPOSED INDICATIONS FOR USE

Dexfenfluramine hydrochloride is indicated for the managemnet of obesity in patients on a reduced calorie diet with an initial Body Mass Index (BMI) of ≥ 27 kg/m^2

LIST NUMBERS OF ALL INVESTIGATIONAL NEW DRUG APPLICATIONS (21 CFR Part 312), NEW DRUG OR ANTIBIOTIC APPLICATIONS (21 CFR Part 314), AND DRUG MASTER FILES (21 CFR 314.420) REFERRED TO IN THIS APPLICATION:

INFORMATION ON APPLICATION

TYPE OF APPLICATION (Check one)

☒ THIS SUBMISSION IS A FULL APPLICATION (21 CFR 314.50) ☐ THIS SUBMISSION IS AN ABBREVIATED APPLICATION (ANDA) (21 CFR 314.55)

IF AN ANDA, IDENTIFY THE APPROVED DRUG PRODUCT THAT IS THE BASIS FOR THE SUBMISSION

NAME OF DRUG	HOLDER OF APPROVED APPLICATION

TYPE SUBMISSION (Check one)

☐ PRESUBMISSION ☒ AN AMENDMENT TO A PENDING APPLICATION ☐ SUPPLEMENTAL APPLICATION
☐ ORIGINAL APPLICATION ☐ RESUBMISSION

SPECIFIC REGULATION(S) TO SUPPORT CHANGE OF APPLICATION (e.g., Part 314.70(b)(2)(iv)) _____

PROPOSED MARKETING STATUS (Check one)

☒ APPLICATION FOR A PRESCRIPTION DRUG PRODUCT (Rx) ☐ APPLICATION FOR AN OVER-THE-COUNTER PRODUCT (OTC)

INDEX02 -1 CAT. SAS ✓ for last.

% of Patients Achieving Weight Loss at Endpoint by Category - Month 12

TABLE OF DRUG BY CAT

DRUG(Drug 0=Placebo,1=Dexfen) CAT

Frequency / Percent / Row Pct / Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	78	54	84	46	262
	13.95	9.66	15.03	8.23	46.87
	29.77	20.61	32.06	17.56	
	33.62	47.37	60.00	63.01	
Dexfenfluramine	154	60	56	27	297
	27.55	10.73	10.02	4.83	53.13
	51.85	20.20	18.86	9.09	
	66.38	52.63	40.00	36.99	
Total	232	114	140	73	559
	41.50	20.39	25.04	13.06	100.00

p-value

0.000

0.000

0.000

test

Fisher's Exact (two-tailed)

Chi-Square

Cochran-Mantel Haenszel, adjusting for country

p-value = 0.000 from [Cochran-Mantel-Haenszel test, adjusting for site.]

SEP 13 '95 14:16

INDEY103.1CAT.SAS

Index Study

14:33 Friday, August 4, 1995 1

% of Patients Achieving Weight Loss at Endpoint by Category
Last Value Carried Forward (1)

TABLE OF DRUG BY CAT

DRUG(Drug 0=Placebo,1=Dexfen) CAT

Frequency Percent Row Pct Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	96	103	175	93	467
	10.32	11.08	18.82	10.00	50.22
	20.56	22.06	37.47	19.91	
	34.53	47.25	59.32	66.91	
Dexfenfluramine	182	115	120	46	463
	19.57	12.37	12.90	4.95	49.78
	39.31	24.84	25.92	9.94	
	65.47	52.75	40.68	33.09	
Total	278	218	295	139	930
	29.89	23.44	31.72	14.95	100.00

Frequency Missing = 11

p-value	test
0.000	Fisher's Exact (two-tailed)
0.000	Chi-Square
(0.000)	Cochran-Mantel-Haenszel, adjusting for country

p-value = 0.000 from [Cochran-Mantel-Haenszel test, adjusting for site.]

(1) Month 12 or last value carried forward if a patient prematurely discontinued participation in the study.

SEP 13 '95 14:16

NOBLE TOBACAT SAS

Noble Study no sites

14:41 Friday, August 4, 1995 1

% of Patients Achieving Weight Loss at Endpoint by Category - Week 24

TABLE OF DRUG BY CAT

DRUG(Drug Treatment Group) CAT

Frequency / Percent / Row Pct / Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	2	3	8	10	23
	4.76	7.14	19.05	23.81	54.76
	8.70	13.04	34.78	43.48	
	25.00	33.33	61.54	83.33	
Dexfenfluramine	6	6	5	2	19
	14.29	14.29	11.90	4.76	45.24
	31.58	31.58	26.32	10.53	
	75.00	66.67	38.46	16.67	
Total	8	9	13	12	42
	19.05	21.43	30.95	28.57	100.00

p-value	test
(0.035)	Fisher's Exact (two-tailed)
0.033	Chi-Square
	Cochran-Mantel-Haenszel not done since only 1 site.

p-value = 0.035 from two-tailed Fisher's Exact test.
There is only one site in this study.
Chi-Square test not used because cell sizes too small.

SEP 13 '95 14:16

NOBLE\B3A3CAT.SAS

BEST POSSIBLE COPY

Noble Study

14:43 Friday, August 4, 1995 1

% of Patients Achieving Weight Loss at Endpoint by Category
Last Value Carried Forward (1)

TABLE OF DRUG BY CAT

DRUG(Drug Treatment Group) CAT

Frequency Percent Row Pct Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	2 3.64 7.41 25.00	3 5.45 11.11 30.00	11 20.00 40.74 50.00	11 20.00 40.74 73.33	27 49.09
Dexfenfluramine	6 10.91 21.43 75.00	7 12.73 25.00 70.00	11 20.00 39.29 50.00	4 7.27 14.29 26.67	28 50.91
Total	8 14.55	10 18.18	22 40.00	15 27.27	55 100.00

p-value test
0.078 Fisher's Exact (two-tailed)
0.077 Chi-Square
Cochran-Mantel-Haenszel not done since only 1 site.

p-value = 0.078 from two-tailed Fisher's Exact test.
There is only one site in this study.
Chi-Square test not used because cell sizes too small.

(1) Week 24 or last value carried forward if a patient prematurely discontinued participation in the study.

EFFMCAT.SAS

Effm Study

14:45 Friday, August 4, 1995 1

X of Patients Achieving Weight Loss at Endpoint by Category - Month 12

TABLE OF DRUG BY CAT

DRUG	CAT				
Frequency Percent Row Pct Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Dexfenfluramine	779 66.13 66.13 100.00	252 21.39 21.39 100.00	103 8.74 8.74 100.00	44 3.74 3.74 100.00	1178 100.00
Total	779 66.13	252 21.39	103 8.74	44 3.74	1178 100.00

no statistical testing because only one drug

EFIM2.CAT.SAS

Efim Study

% of Patients Achieving Weight Loss at Endpoint by Category
Last Value Carried Forward (1)

TABLE OF DRUG BY CAT

DRUG	CAT				
Frequency Percent Row Pct Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Dexfenfluramine	910 52.18 52.18 100.00	409 23.45 23.45 100.00	312 17.89 17.89 100.00	113 6.48 6.48 100.00	1744 100.00
Total	910 52.18	409 23.45	312 17.89	113 6.48	1744 100.00

no statistical testing because only one drug.

(1) Month 12 or last value carried forward if a patient prematurely discontinued participation in the study.

SEP 13 '95 14:16

P003TOZAICAT.SAS

P003 Study

X of Patients Achieving Weight Loss at Endpoint by Category - Week 12

TABLE OF DRUG BY CAT

DRUG(Drug Treatment Group) CAT

Frequency / Percent / Row Pct / Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	1	15	26	13	55
	0.89	13.39	23.21	11.61	49.11
	1.82	27.27	47.27	23.64	
	12.50	34.09	65.00	65.00	
30 mg Dexfenflur	7	29	14	7	57
	6.25	25.89	12.50	6.25	50.89
	12.28	50.88	24.56	12.28	
	87.50	65.91	35.00	35.00	
Total	8	44	40	20	112
	7.14	39.29	35.71	17.86	100.00

p-value	test
(0.002)	Fisher's Exact (two-tailed)
0,002	Chi-Square
0,003	Cochran-Mantel-Haenszel, adjusting for center

Multiple sites in this study, but Cochran-Mantel-Haenszel not used since cell sizes too small.

p-value = 0.002 from two-tailed Fisher's exact test.

SEP 13 '95 14:17

P003 DRAGCAT.SAS

P003 Study

% of Patients Achieving Weight loss at Endpoint by Category
Last Value Carried Forward (1)

TABLE OF DRUG BY CAT

DRUG(Drug Treatment Group) CAT

Frequency Percent Row Pct Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	1	15	42	23	81
	0.63	9.49	26.58	14.56	51.27
	1.23	18.52	51.85	28.40	
	12.50	31.91	60.87	67.65	
30 mg Dexfenflur	7	32	27	11	77
	4.43	20.25	17.09	6.96	48.73
	9.09	41.56	35.06	14.29	
	87.50	68.09	39.13	32.35	
Total	8	47	69	34	158
	5.06	29.75	43.67	21.52	100.00

Frequency Missing = 1

p-value test
(0.000) Fisher's Exact (two-tailed)
0.000 Chi-Square
0.001 Cochran-Mantel-Haenszel, adjusting for center

Multiple sites in this study, but Cochran-Mantel-Haenszel not used since cell sizes too small.
p-value = 0.000 from two-tailed Fisher's Exact test.

(1) Week 12 or last value carried forward if a patient prematurely discontinued participation in the study.

SEP 13 '95 14:17

P005 1S3 AECAT.SAS

P005 Study

14:59 Friday, August 4, 1995 1

% of Patients Achieving Weight Loss at Endpoint by Category - Week 12

TABLE OF DRUG BY CAT

DRUG(Drug Treatment Group) CAT

Frequency Percent Row Pct Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	4	17	48	36	105
	1.83	7.76	21.92	16.44	47.95
	3.81	16.19	45.71	34.29	
	18.18	26.98	53.33	81.82	
30 mg Dexfenflur	18	46	42	8	114
	8.22	21.00	19.18	3.65	52.05
	15.79	40.35	36.84	7.02	
	81.82	73.02	46.67	18.18	
Total	22	63	90	44	219
	10.05	28.77	41.10	20.09	100.00

p-value	test
0.000	Fisher's Exact (two-tailed)
0.000	Chi-Square
(0.000)	Cochran-Mantel-Haenszel, adjusting for center

p-value = 0.000 from [Cochran-Mantel-Haenszel test, adjusting for site]

SEP 13 '95 14:17

P005 TOT RAW CAT.SAS

P005 Study

% of Patients Achieving Weight Loss at Endpoint by Category
Last Value Carried Forward (1)

TABLE OF DRUG BY CAT

DRUG(Drug Treatment Group) CAT

Frequency Percent Row Pct Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	4	19	79	58	160
	1.26	5.97	24.84	18.24	50.31
	2.50	11.88	49.38	36.25	
	17.39	27.94	51.97	77.33	
30 mg Dexfenflur	19	49	73	17	158
	5.97	15.41	22.96	5.35	49.69
	12.03	31.01	46.20	10.76	
	82.61	72.06	48.03	22.67	
Total	23	68	152	75	318
	7.23	21.38	47.80	23.58	100.00

Frequency Missing = 3

p-value	test
0.000	Fisher's Exact (two-tailed)
0.000	Chi-Square
0.000	Cochran-Mantel-Haenszel, adjusting for center

p-value = 0.000 from [Cochran-Mantel-Haenszel test, adjusting for site]

(1) Week 12 or last value carried forward if a patient prematurely discontinued participation in the study.

SEP 13 '95 14:17

UK18TOTALCAT.SAS

UK18 Study

15:03 Friday, August 4, 1995 1

% of Patients Achieving Weight Loss at Endpoint by Category - Week 26

TABLE OF DRUG BY CAT

DRUG(Drug-Tx Group)	CAT				
Frequency Percent Row Pct Col Pct	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	0 0.00 0.00 0.00	1 3.13 6.25 20.00	4 12.50 25.00 44.44	11 34.38 68.75 78.57	16 50.00
Dexfenfluramine	4 12.50 25.00 100.00	4 12.50 25.00 80.00	5 15.63 31.25 55.56	3 9.38 18.75 21.43	16 50.00
Total	4 12.50	5 15.63	9 28.13	14 43.75	32 100.00

p-value	test
0.011	Fisher's Exact (two-tailed)
0.015	Chi-Square
	Cochran-Mantel-Haenszel not done since only 1 site

p-value = 0.011 from two-tailed Fisher's Exact test.
There is only one site in this study.
Chi-Square test not used because cell sizes too small.

UK18TOTA2CAT.SAS

UK18 Study

15:04 Friday, August 4, 1995 1

% of Patients Achieving Weight Loss at Endpoint by Category
Last Value Carried Forward (1)

TABLE OF DRUG BY CAT

DRUG(Drug-Tx Group) / CAT	> 10%	>5% - 10%	>0% - 5%	<=0%	Total
Placebo	0	1	6	13	20
	0.00	2.38	14.29	30.95	47.62
	0.00	5.00	30.00	65.00	
	0.00	20.00	40.00	72.22	
Dexfenfluramine	4	4	9	5	22
	9.52	9.52	21.43	11.90	52.38
	18.18	18.18	40.91	22.73	
	100.00	80.00	60.00	27.78	
Total	4	5	15	18	42
	9.52	11.90	35.71	42.86	100.00

p-value	test
0.014	Fisher's Exact (two-tailed)
0.020	Chi-Square
	Cochran-Mantel-Haenszel not done since only 1 site

p-value = 0.014 from two-tailed Fisher's Exact test.
There is only one site in this study.
Chi-Square test not used because cell sizes too small.

(1) Week 26 or last value carried forward if a patient prematurely discontinued participation in the study.

"RESPONDER" ANALYSIS

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT1

DRUG(Drug 0=Placebo,1=Dexfen)

	RESULT(5% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	267 28.71 57.17 61.66	200 21.51 42.83 40.24	467 50.22
Dexfenfluramine	166 17.85 35.85 38.34	297 31.94 64.15 59.76	463 49.78
Total	433 46.56	497 53.44	930 100.00

Frequency Missing = 11

p-value	test
0.000	Fisher's Exact (two-tailed)
0.000	Chi-Square
0.000	Cochran-Mantel-Haenszel, adjusting for country

(1) Month 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT2

DRUG(Drug 0=Placebo, 1=Dexfen)

	RESULT2(10% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	371 39.89 79.44 56.99	96 10.32 20.56 34.41	467 50.22
Dexfenfluramine	280 30.11 60.48 43.01	183 19.68 39.52 65.59	463 49.78
Total	651 70.00	279 30.00	930 100.00

Frequency Missing = 11

p-value	test
0.000	Fisher's Exact (two-tailed)
0.000	Chi-Square
0.000	Cochran-Mantel-Haenszel, adjusting for Country

(1) Month 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT3

DRUG(Drug 0=Placebo,1=Dexfen)

	RESULT3(15% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	418 44.95 89.51 53.38	49 5.27 10.49 33.33	467 50.22
Dexfenfluramine	365 39.25 78.83 46.62	98 10.54 21.17 66.67	463 49.78
Total	783 84.19	147 15.81	930 100.00

Frequency Missing = 11

p-value	test
0.000	Fisher's Exact (two-tailed)
0.000	Chi-Square
0.000	Cochran-Mantel-Haenszel, adjusting for Country

(1) Month 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT1

DRUG(Drug Treatment Group)
RESULT1(5% Loss)

Frequency / Percent / Row Pct / Col Pct	Failure	Success	Total
Placebo	22	5	27
	40.00	9.09	49.09
	81.48	18.52	
	59.46	27.78	
Dexfenfluramine	15	13	28
	27.27	23.64	50.91
	53.57	46.43	
	40.54	72.22	
Total	37	18	55
	67.27	32.73	100.00

p-value — test

0.044 — Fisher's Exact (two-tailed)

(0.027) — Chi-Square

Cochran-Mantel-Haenszel not done since only 1 site

(1) Week 24 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT2

DRUG(Drug Treatment Group)
RESULT2(10% Loss)

Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	25	2	27
	45.45	3.64	49.09
	92.59	7.41	
	53.19	25.00	
Dexfenfluramine	22	6	28
	40.00	10.91	50.91
	78.57	21.43	
	46.81	75.00	
Total	47	8	55
	85.45	14.55	100.00

p-value	test
0.252	Fisher's Exact (two-tailed)
0.140	Chi-Square

Cochran-Mantel-Haenszel not done since only 1 site

(1) Week 24 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT3

DRUG(Drug Treatment Group)
RESULT3(15% Loss)

Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	25	2	27
	45.45	3.64	49.09
	92.59	7.41	
	47.17	100.00	
Dexfenfluramine	28	0	28
	50.91	0.00	50.91
	100.00	0.00	
	52.83	0.00	
Total	53	2	55
	96.36	3.64	100.00

p-value — test
0.236 — Fisher's Exact (two-tailed)
0.142 — Chi-Square
Cochran-Mantel-Haenszel not done since only 1 site

(1) Week 24 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT1

DRUG	RESULT1(5% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Dexfenfluramine	425 24.37 24.37 100.00	1319 75.63 75.63 100.00	1744 100.00
Total	425 24.37	1319 75.63	1744 100.00

(1) Month 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT2

DRUG	RESULT2(10% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Dexfenfluramine	828 47.48 47.48 100.00	916 52.52 52.52 100.00	1744 100.00
Total	828 47.48	916 52.52	1744 100.00

(1) Month 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT3

DRUG	RESULT3(15% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Dexfenfluramine	1249 71.62 71.62 100.00	495 28.38 28.38 100.00	1744 100.00
Total	1249 71.62	495 28.38	1744 100.00

(1) Month 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight loss at endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT1

DRUG(Drug Treatment Group)

	RESULT1(5% Loss)		
Frequency			
Percent			
Row Pct			
Col Pct	Failure	Success	Total
Placebo	65	16	81
	41.14	10.13	51.27
	80.25	19.75	
	63.11	29.09	
30 mg Dexfenflur	38	39	77
	24.05	24.68	48.73
	49.35	50.65	
	36.89	70.91	
Total	103	55	158
	65.19	34.81	100.00

Frequency Missing = 1

p-value test
0.000 Fisher's Exact (2-tailed)
0.000 Chi-Square
0.000 CMH, adjusting for center

(1) Week 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight loss at endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT2

DRUG(Drug Treatment Group)

	RESULT2(10% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	80 50.63 98.77 53.69	1 0.63 1.23 11.11	81 51.27
30 mg Dexfenflur	69 43.67 89.61 46.31	8 5.06 10.39 88.89	77 48.73
Total	149 94.30	9 5.70	158 100.00

Frequency Missing = 1

p-value	test
0.016	Fisher's Exact (2-tailed)
0.013	Chi-Square
0.013	CMH, adjusting for center

(1) Week 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight loss at endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT3

DRUG(Drug Treatment Group)

	RESULT3(15% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	81 51.27 100.00 51.59	0 0.00 0.00 0.00	81 51.27
30 mg Dexfenflur	76 48.10 98.70 48.41	1 0.63 1.30 100.00	77 48.73
Total	157 99.37	1 0.63	158 100.00

Frequency Missing = 1

p-value	test
(0.487)	Fisher's Exact (2-tailed)
0.304	Chi-Square
0.317	CMH, adjusting for center

(1) Week 12 or last value carried forward if a patient prematurely discontinued participation in the study.

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% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT1

DRUG(Drug Treatment Group)

	RESULT1(5% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	137 43.08 85.63 60.35	23 7.23 14.38 25.27	160 50.31
30 mg Dexfenflur	90 28.30 56.96 39.65	68 21.38 43.04 74.73	158 49.69
Total	227 71.38	91 28.62	318 100.00

Frequency Missing = 3

p-value	test
0.000	Fisher's Exact (2-Tailed)
0.000	Chi-Square
(0.000)	CMH, adjusting for center

(1) Week 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT2

DRUG(Drug Treatment Group)

	RESULT2(10% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	156 49.06 97.50 53.06	4 1.26 2.50 16.67	160 50.31
30 mg Dexfenflur	138 43.40 87.34 46.94	20 6.29 12.66 83.33	158 49.69
Total	294 92.45	24 7.55	318 100.00

Frequency Missing = 3

p-value	test
0.001	Fisher's Exact (2-tailed)
0.001	Chi-Square
0.001	CMH, adj. for center

(1) Week 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT3

DRUG(Drug Treatment Group)

	RESULT3(15% Loss)		
Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	160 50.31 100.00 50.79	0 0.00 0.00 0.00	160 50.31
30 mg Dexfenflur	155 48.74 98.10 49.21	3 0.94 1.90 100.00	158 49.69
Total	315 99.06	3 0.94	318 100.00

Frequency Missing = 3

p-value	test
(0.121)	Fisher's Exact (2-tailed)
0.080	Chi-Square
0.083	CMH, adj. for center

(1) Week 12 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT1

DRUG(Drug-Tx Group) RESULT1(5% Loss)

Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	19	1	20
	45.24	2.38	47.62
	95.00	5.00	
	57.58	11.11	
Dexfenfluramine	14	8	22
	33.33	19.05	52.38
	63.64	36.36	
	42.42	88.89	
Total	33	9	42
	78.57	21.43	100.00

p-value test
0.022 Fisher's Exact (two-tailed)
0.013 Chi-Square
Cochran-Mantel-Haenszel not done since only 1 site

(1) Week 26 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT2

DRUG(Drug-Tx Group) RESULT2(10% Loss)

Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	20	0	20
	47.62	0.00	47.62
	100.00	0.00	
	52.63	0.00	
Dexfenfluramine	18	4	22
	42.86	9.52	52.38
	81.82	18.18	
	47.37	100.00	
Total	38	4	42
	90.48	9.52	100.00

p-value	test
(0.109)	Fisher's Exact (two-tailed)
0.045	Chi-Square
	Cochran-Mantel-Haenszel not done since only 1 site

(1) Week 26 or last value carried forward if a patient prematurely discontinued participation in the study.

% of Patients Achieving 5%-15% Weight Loss at Endpoint
Last Value Carried Forward (1)

TABLE OF DRUG BY RESULT3

DRUG(Drug-Tx Group) RESULT3(15% Loss)

Frequency Percent Row Pct Col Pct	Failure	Success	Total
Placebo	20	0	20
	47.62	0.00	47.62
	100.00	0.00	
	50.00	0.00	
Dexfenflu-amine	20	2	22
	47.62	4.76	52.38
	90.91	9.09	
	50.00	100.00	
Total	40	2	42
	95.24	4.76	100.00

p-value test
0.489 Fisher's Exact (two-tailed)
0.167 Chi-Square
Cochran-Mantel-Haenszel not done since only 1 site.

(1) Week 26 or last value carried forward if a patient prematurely discontinued participation in the study.

DIASTOLIC BLOOD PRESSURE

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

		Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
AGE yrs (1)				
N		227	220	0.2552
Mean		42.4	43.5	
Std. Dev.		12.2	11.9	
Minimum				
Maximum				
SEX				
Male	N (%)	55 (24.2)	50 (22.7)	0.8482
Female	N (%)	172 (75.8)	170 (77.3)	
ETHNIC ORIGIN				
Caucasian	N (%)	218 (96.0)	213 (96.8)	0.0153
Black	N (%)	3 (1.3)	7 (3.2)	
Other	N (%)	6 (2.6)	0	
Not Specified	N (%)	0	0	

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

		Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
TOBACCO HABIT				
Non-Smoker	N (%)	158 (69.6)	157 (71.4)	0.7845
Moderate Use	N (%)	50 (22.0)	47 (21.4)	
Heavy Use	N (%)	19 (8.4)	16 (7.3)	
ALCOHOL				
No Intake	N (%)	112 (49.3)	110 (50.0)	0.9844
Moderate Intake	N (%)	114 (50.2)	109 (49.5)	
Heavy Intake	N (%)	1 (0.4)	1 (0.5)	
DURATION OF OBESITY (yrs) (2) (3)				
N		214	204	0.3625
Mean		20.9	19.9	
Std. Dev.		11.6	11.4	
Minimum				
Maximum				

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

		Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
ONSET OF OBESITY				
Childhood	N (%)	66 (29.1)	51 (23.2)	0.2380
Adolescence	N (%)	23 (10.1)	21 (9.5)	
Adulthood	N (%)	138 (60.8)	148 (67.3)	
FAMILY HISTORY OF OBESITY				
None	N (%)	44 (19.4)	58 (26.4)	0.0727
Father	N (%)	84 (37.0)	66 (30.0)	0.1135
Mother	N (%)	112 (49.3)	116 (52.7)	0.4763
Sibling	N (%)	78 (34.4)	69 (31.4)	0.4327
Offspring	N (%)	29 (12.8)	32 (14.5)	0.5341
CAUSE OF OBESITY				
Hypercorticism	N (%)	0	0	
Hyperthyroidism	N (%)	1 (0.4)	0	
Other	N (%)	101 (44.5)	104 (47.3)	
Not Specified	N (%)	125 (55.1)	116 (52.7)	

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

Interneuron Pharmaceuticals, Inc.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

Index Study

		Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
PREVIOUS TREATMENT FOR OBESITY				
Yes	N (%)	187 (82.4)	187 (85.0)	0.5499
No	N (%)	40 (17.6)	33 (15.0)	
NATURE OF PREVIOUS TREATMENT FOR OBESITY				
Diet				
Yes	N (%)	171 (91.4)	174 (93.0)	0.6407
No	N (%)	16 (8.6)	13 (7.0)	
Not Specified	N (%)	0	0	
Behavior				
Yes	N (%)	17 (9.1)	13 (7.0)	0.4477
No	N (%)	170 (90.9)	174 (93.0)	
Not Specified	N (%)	0	0	
Drug Therapy				
Yes	N (%)	98 (52.4)	94 (50.3)	0.4877
No	N (%)	89 (47.6)	93 (49.7)	
Not Specified	N (%)	0	0	

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

Interneuron Pharmaceuticals, Inc.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

Index Study

		Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
NATURE OF PREVIOUS TREATMENT FOR OBESITY				
Other				
Yes	N (%)	9 (4.8)	8 (4.3)	0.7232
No	N (%)	178 (95.2)	179 (95.7)	
Not Specified	N (%)	0	0	
HEIGHT (cm) (2)				
N		226	220	0.4756
Mean		166.0	165.5	
Std. Dev.		9.2	9.1	
Minimum				
Maximum				
MAXIMUM ADULT WEIGHT EVER (kg) (2)				
N		227	220	0.6069
Mean		105.9	105.2	
Std. Dev.		22.8	20.0	
Minimum				
Maximum				

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

Interneuron Pharmaceuticals, Inc.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

Index Study

	Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
WEIGHT LOSS OBJECTIVE (kg) (2) (3)			
N	213	204	0.4315
Mean	62.5	62.1	
Std. Dev.	6.1	5.9	
Minimum			
Maximum			
SCREEN WEIGHT (kg) (2) (3)			
N	213	204	0.6733
Mean	102.6	101.9	
Std. Dev.	22.6	19.8	
Minimum			
Maximum			
PERCENT OF IDEAL WEIGHT (SCREEN) (2) (3)			
N	213	204	0.9677
Mean	163.6	163.8	
Std. Dev.	28.9	26.2	
Minimum			
Maximum			

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

Interneuron Pharmaceuticals, Inc.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

Index Study

	Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
PRESENT WEIGHT (BASELINE) (kg) (2) (3)			
N	214	204	0.6705
Mean	102.8	102.0	
Std. Dev.	22.5	19.8	
Minimum			
Maximum			
PERCENT OF IDEAL WEIGHT (BASELINE) (2) (3)			
N	214	204	0.9851
Mean	163.9	164.0	
Std. Dev.	29.0	26.2	
Minimum			
Maximum			
AMOUNT OVERWEIGHT (SCREEN) (kg) (2) (3)			
N	214	203	0.9055
Mean	40.2	40.1	
Std. Dev.	19.8	17.1	
Minimum			
Maximum			

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

Interneuron Pharmaceuticals, Inc.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

Index Study

	Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
CHANGE IN WEIGHT FROM SCREEN TO BASELINE (kg) (2) (3)			
N	213	204	0.8156
Mean	0.2	0.2	
Std. Dev.	1.8	2.3	
Minimum			
Maximum			
AMOUNT OVERWEIGHT (BASELINE) (kg) (2) (3)			
N	214	203	0.9055
Mean	40.2	40.1	
Std. Dev.	19.8	17.1	
Minimum			
Maximum			
BODY MASS INDEX (BASELINE) (kg/m2) (2) (3)			
N	213	204	0.9375
Mean	37.2	37.2	
Std. Dev.	6.5	5.9	
Minimum			
Maximum			

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

	Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
WAIST (BASELINE) (cm) (2) (3)			
N	209	197	0.6033
Mean	112.0	112.6	
Std. Dev.	15.0	14.4	
Minimum			
Maximum			
HIPS (BASELINE) (cm) (2) (3)			
N	209	196	0.2220
Mean	116.8	119.1	
Std. Dev.	20.3	19.2	
Minimum			
Maximum			
WAIST/HIP RATIO (BASELINE) (2) (3)			
N	209	196	0.3911
Mean	1.0	1.0	
Std. Dev.	0.3	0.2	
Minimum			
Maximum			

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

PATIENT DEMOGRAPHIC AND BACKGROUND DATA

Baseline Sitting or Supine Diastolic Blood Pressure >= 90

Index Study

		Dexfenfluramine (N=227)	Placebo (N=220)	P-Value (1)
PREVIOUS PREGNANCIES				
0 Pregnancies	N (%)	44 (25.6)	26 (15.3)	0.0557
1 Pregnancy	N (%)	31 (18.0)	35 (20.6)	
2 Pregnancies	N (%)	46 (26.7)	41 (24.1)	
3+ Pregnancies	N (%)	51 (29.7)	68 (40.0)	
Not Specified	N (%)	0	0	
PHYSICAL ACTIVITY				
None	N (%)	69 (30.4)	81 (36.8)	0.1668
Little	N (%)	131 (57.7)	113 (51.4)	
Much	N (%)	26 (11.5)	26 (11.8)	
Not Specified	N (%)	1 (0.4)	0	

(1) P-value for treatment group assignment for continuous variables from an analysis of variance model with effects for treatment group assignment and country. P-value for treatment group assignment for categorical variables from a Cochran-Mantel-Haenszel test controlling for country. P-value for treatment group assignment for Ethnic Origin and Previous Pregnancies from a two-tailed Fisher's Exact test.

(2) P-value for treatment group assignment effect from an analysis of variance model with effects for treatment group assignment, country, and stratum.

(3) Anthropometric measurements for patients who had no assessments when study medication was first prescribed are not included.

Intent-to-Treat Analysis
Index Study

VITAL SIGNS - CHANGE FROM BASELINE
Patients with Baseline Sitting or Supine Diastolic Blood Pressure >= 90
Sitting and Supine Blood Pressure Combined - Last Value Carried Forward (1)

	Dexfenfluramine				Placebo			
	Baseline	Month 1	Month 2	Month 4	Baseline	Month 1	Month 2	Month 4
Systolic Blood Pressure (mm Hg)								
N	227	212	211	211	220	208	205	207
Mean	151.2	-12.9	-13.0	-15.5	150.4	-7.8	-8.5	-10.9
Std. Dev.	19.4	19.2	19.0	19.4	16.9	16.8	16.9	18.4
Minimum								
Maximum								
P-Value (2)		0.0044	0.0115	0.0133				
Diastolic Blood Pressure (mm Hg)								
N	227	212	211	211	220	208	205	207
Mean	98.5	-10.4	-10.9	-12.6	97.6	-6.6	-6.9	-8.7
Std. Dev.	9.8	11.2	11.7	12.1	9.2	10.5	11.6	12.4
Minimum								
Maximum								
P-Value (2)		0.0004	0.0004	0.0012				

(1) Last value carried forward if a patient prematurely terminated participation in the study.
(2) P-value from an analysis of variance model with effects for treatment; this is a post-hoc analysis, no adjustments to p-value were made

VITAL SIGNS - CHANGE FROM BASELINE

Patients with Baseline Sitting or Supine Diastolic Blood Pressure >= 90

Sitting and Supine Blood Pressure Combined - Last Value Carried Forward (1)

Intent-to-Treat Analysis

Index Study

	Dexfenfluramine				Placebo			
	Month 6	Month 8	Month 10	Month 12	Month 6	Month 8	Month 10	Month 12
Systolic Blood Pressure (mm Hg)								
N	209	207	207	213	208	204	206	208
Mean	-16.3	-17.0	-16.9	-14.8	-12.1	-10.5	-12.3	-11.9
Std. Dev.	19.6	20.6	20.1	21.0	19.5	21.1	21.0	19.9
Minimum								
Maximum								
P-Value (2)	0.0274	0.0274	0.6582	0.1584				
Diastolic Blood Pressure (mm Hg)								
N	209	206	207	213	208	204	206	208
Mean	-12.3	-12.2	-12.8	-12.5	-10.2	-8.0	-9.4	-9.9
Std. Dev.	12.4	11.5	13.3	12.3	13.9	13.3	12.3	13.3
Minimum								
Maximum								
P-Value (2)	0.0955	0.0955	0.3091	0.0425				

(1) Last value carried forward if a patient prematurely terminated participation in the study.

(2) P-value from an analysis of variance model with effects for treatment; this is a post-hoc analysis, no adjustments to p-value were made.

Intent-to-Treat Analysis
Index Study

VITAL SIGNS - CHANGE FROM BASELINE
Patients with Baseline Sitting or Supine Diastolic Blood Pressure >= 90
Last Value Carried Forward (1)

	Dexfenfluramine				Placebo			
	Baseline	Month 1	Month 2	Month 4	Baseline	Month 1	Month 2	Month 4
Sitting Systolic Blood Pressure (mm Hg)								
N	172	161	161	162	167	156	153	156
Mean	150.7	-12.8	-13.5	-16.4	150.8	-8.4	-8.2	-11.4
Std. Dev.	20.1	19.3	19.4	20.1	16.8	16.6	16.1	17.9
Minimum								
Maximum								
P-Value (2)		0.0295	0.0100	0.0212				
Sitting Diastolic Blood Pressure (mm Hg)								
N	172	161	161	162	167	156	153	156
Mean	98.7	-10.3	-11.2	-12.8	98.0	-6.5	-6.8	-9.0
Std. Dev.	10.2	10.9	11.6	12.0	9.2	10.4	11.4	12.4
Minimum								
Maximum								
P-Value (2)		0.0017	0.0008	0.0053				

(1) Last value carried forward if a patient prematurely terminated participation in the study.
(2) P-value from an analysis of variance model with effects for treatment; this is a post-hoc analysis, no adjustments to p-values were made.

Intent-to-Treat Analysis
Index Study

VITAL SIGNS - CHANGE FROM BASELINE
Patients with Baseline Sitting or Supine Diastolic Blood Pressure >= 90
Last Value Carried Forward (1)

	Dexfenfluramine				Placebo			
	Month 6	Month 8	Month 10	Month 12	Month 6	Month 8	Month 10	Month 12
Sitting Systolic Blood Pressure (mm Hg)								
N	161	159	157	162	156	153	154	156
Mean	-17.3	-18.0	-18.1	-15.7	-12.9	-11.8	-13.5	-13.0
Std. Dev.	20.2	20.9	21.1	21.7	20.2	21.3	21.2	20.4
Minimum								
Maximum								
P-Value (2)	0.0515	0.0515	0.9541	0.2552				
Sitting Diastolic Blood Pressure (mm Hg)								
N	161	158	157	162	156	153	154	156
Mean	-12.7	-11.7	-12.7	-12.5	-11.1	-8.7	-10.1	-10.3
Std. Dev.	12.6	11.4	13.7	12.4	14.1	13.4	12.7	13.5
Minimum								
Maximum					-- -			
P-Value (2)	0.2907	0.2907	0.4742	0.1237				

(1) Last value carried forward if a patient prematurely terminated participation in the study.
(2) P-value from an analysis of variance model with effects for treatment; this is a post-hoc analysis, no adjustments to p-values were made.

VITAL SIGNS - CHANGE FROM BASELINE
Patients with Baseline Sitting or Supine Diastolic Blood Pressure >= 90
Last Value Carried Forward (1)

	Dexfenfluramine				Placebo			
	Baseline	Month 1	Month 2	Month 4	Baseline	Month 1	Month 2	Month 4
Supine Systolic Blood Pressure (mm Hg)								
N	55	51	50	49	53	52	52	51
Mean	152.8	-13.1	-11.4	-12.7	149.3	-6.3	-9.3	-9.4
Std. Dev.	16.9	19.0	17.8	16.5	17.4	17.4	19.2	20.0
Minimum								
Maximum								
P-Value (2)		0.0575	0.5597	0.3713				
Supine Diastolic Blood Pressure (mm Hg)								
N	55	51	50	49	53	52	52	51
Mean	97.6	-10.6	-10.1	-12.0	96.2	-6.7	-7.2	-7.9
Std. Dev.	8.6	12.2	12.0	12.3	9.1	11.1	12.3	12.4
Minimum								
Maximum								
P-Value (2)		0.0965	0.2209	0.1041				

(1) Last value carried forward if a patient prematurely terminated participation in the study.
(2) P-value from an analysis of variance model with effects for treatment; this is a post-hoc analysis, no adjustments to p-values were made.

VITAL SIGNS - CHANGE FROM BASELINE
Patients with Baseline Sitting or Supine Diastolic Blood Pressure >= 90
Last Value Carried Forward (1)

	Dexfenfluramine				Placebo			
	Month 6	Month 8	Month 10	Month 12	Month 6	Month 8	Month 10	Month 12
Supine Systolic Blood Pressure (mm Hg)								
N	48	48	50	51	52	51	52	52
Mean	-13.1	-13.7	-12.9	-11.8	-9.8	-6.9	-8.7	-8.8
Std. Dev.	17.2	19.5	16.4	18.4	17.5	20.2	20.0	18.0
Minimum								
Maximum								
P-Value (2)	0.3396	0.3396	0.2893	0.4025				
Supine Diastolic Blood Pressure (mm Hg)								
N	48	48	50	51	52	51	52	52
Mean	-11.2	-13.9	-13.0	-12.2	-7.5	-5.9	-7.3	-8.8
Std. Dev.	11.4	11.9	12.2	12.2	12.7	12.8	11.1	12.6
Minimum								
Maximum								
P-Value (2)	0.1308	0.1308	0.4035	0.1652				

(1) Last value carried forward if a patient prematurely terminated participation in the study.
(2) P-value from an analysis of variance model with effects for treatment; this is a post-hoc analysis, no adjustments to p-values were made.

EFIM STUDY
(LOCF)

TABLE 2X

ANTHROPOMETRIC MEASUREMENTS - CHANGE FROM BASELINE - LAST VALUE CARRIED FORWARD (1)

Dexfenfluramine

	Baseline	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12
Weight (kg)								
N	1744	1744	1734	1728	1738	1734	1735	1744
Mean	84.5	-3.2	-5.1	-6.6	-7.6	-8.2	-8.7	-9.2
Std. Dev.	14.4	2.6	3.7	4.7	5.4	6.0	6.6	7.0
Minimum								
Maximum								

(1) For patients who prematurely terminated participation in the study, all analyses are based upon last value carried forward.

TABLE 2X

Interneuron Pharmaceuticals, Inc.
Intent-to-Treat Analysis
Efim Study

ANTHROPOMETRIC MEASUREMENTS - % WEIGHT CHANGE - LAST VALUE CARRIED FORWARD (1)

Dexfenfluramine

	Baseline	Month 1	Month 2	Month 4	Month 6	Month 8	Month 10	Month 12
Weight (kg)								
N	1744	1744	1734	1728	1738	1734	1735	1744
Mean	84.5	-3.8	-6.0	-7.8	-9.0	-9.8	-10.4	-10.9
Std. Dev.	14.4	2.9	4.1	5.2	6.1	6.7	7.3	7.7
Minimum								
Maximum								

(1) For patients who prematurely terminated participation in the study, all analyses are based upon last value carried forward.

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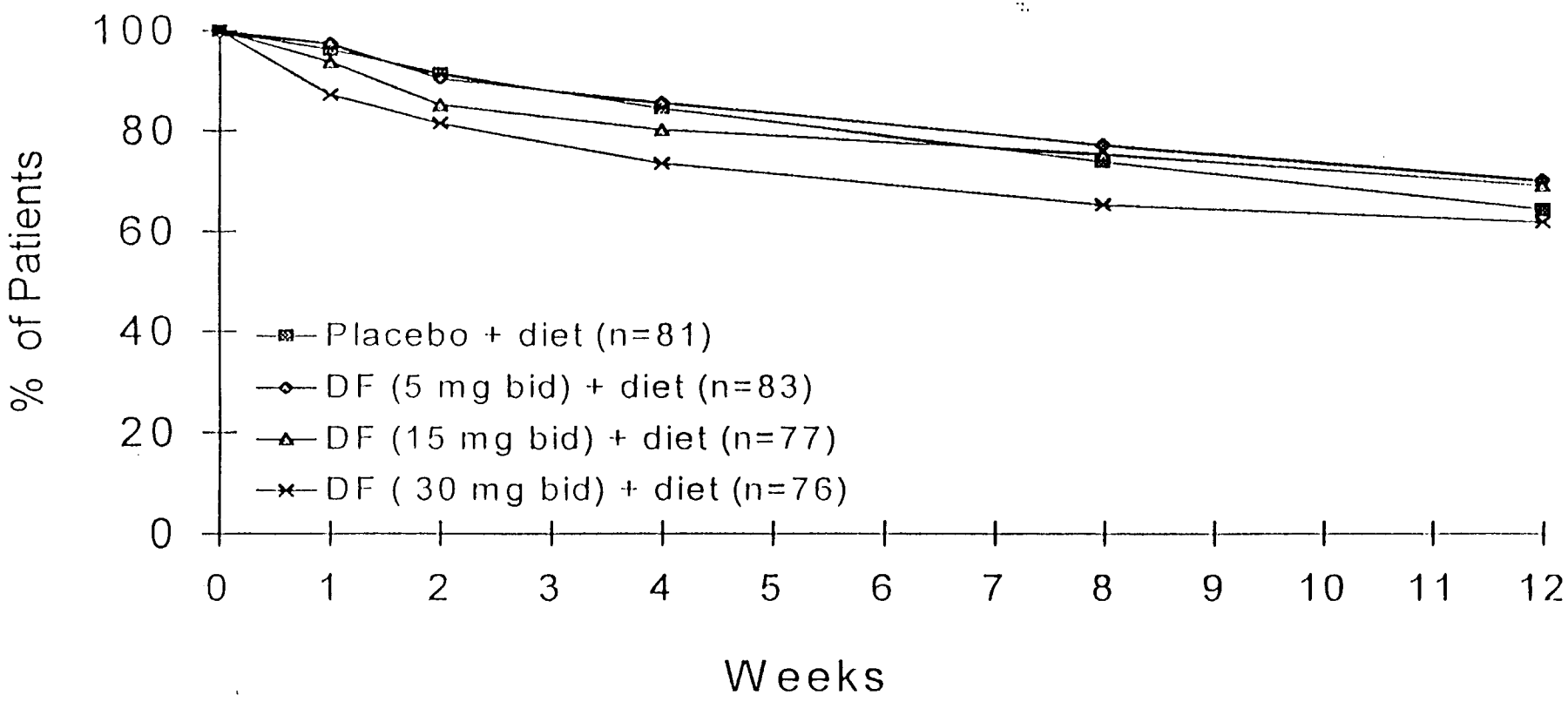
PERCENT COMPLETERS

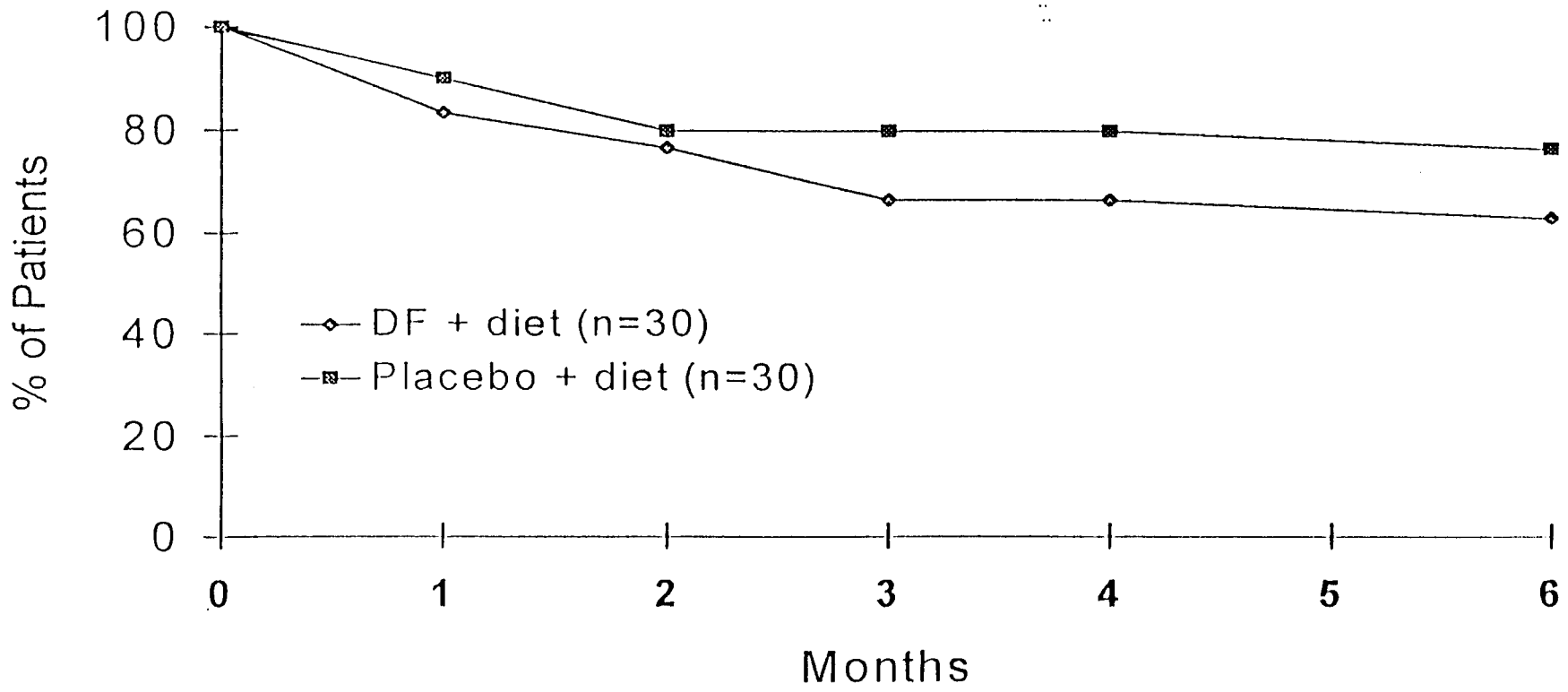
Percentage of Patients on Study- IP92-003



All patient

Drug	Week	Total N	% Patients on Study
Placebo	0	85	100
	1	82	96.4
	2	78	91.7
	4	72	84.7
	8	63	74.1
	12	55	64.7
DF	0	85	100
	1	83	97.6
	2	77	90.6
	4	73	85.9
	8	66	77.6
	12	60	70.6
30 mg DF	0	82	100
	1	77	93.9
	2	70	85.4
	4	66	80.4
	8	62	75.6
	12	57	69.5
60 mg DF	0	87	100
	1	76	87.4
	2	71	81.6
	4	64	73.6
	8	57	65.5
	12	54	62.1

Percentage of Patients on Study - Noble

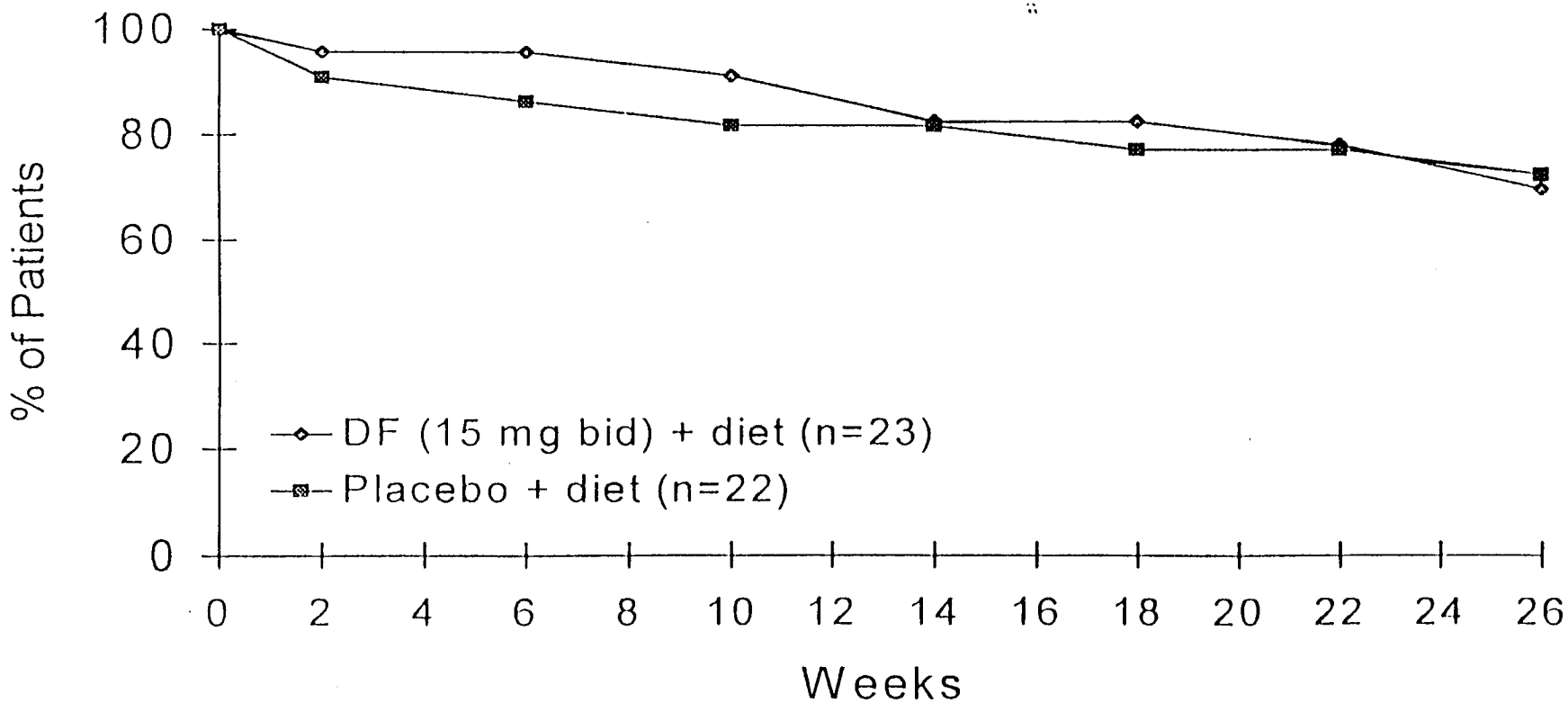


All patient

Noble Study:

Drug	Week	Total N	% Patients on Study
Placebo	0	30	100
	1	27	90.0
	2	27	90.0
	4	27	90.0
	8	24	80.0
	12	24	80.0
	16	24	80.0
	24	23	76.7
DF	0	30	100
	1	28	93.3
	2	27	90.0
	4	25	83.3
	8	23	76.7
	12	20	66.7
	16	20	66.7
	24	19	63.3

Percentage of Patients on Study - UK 18

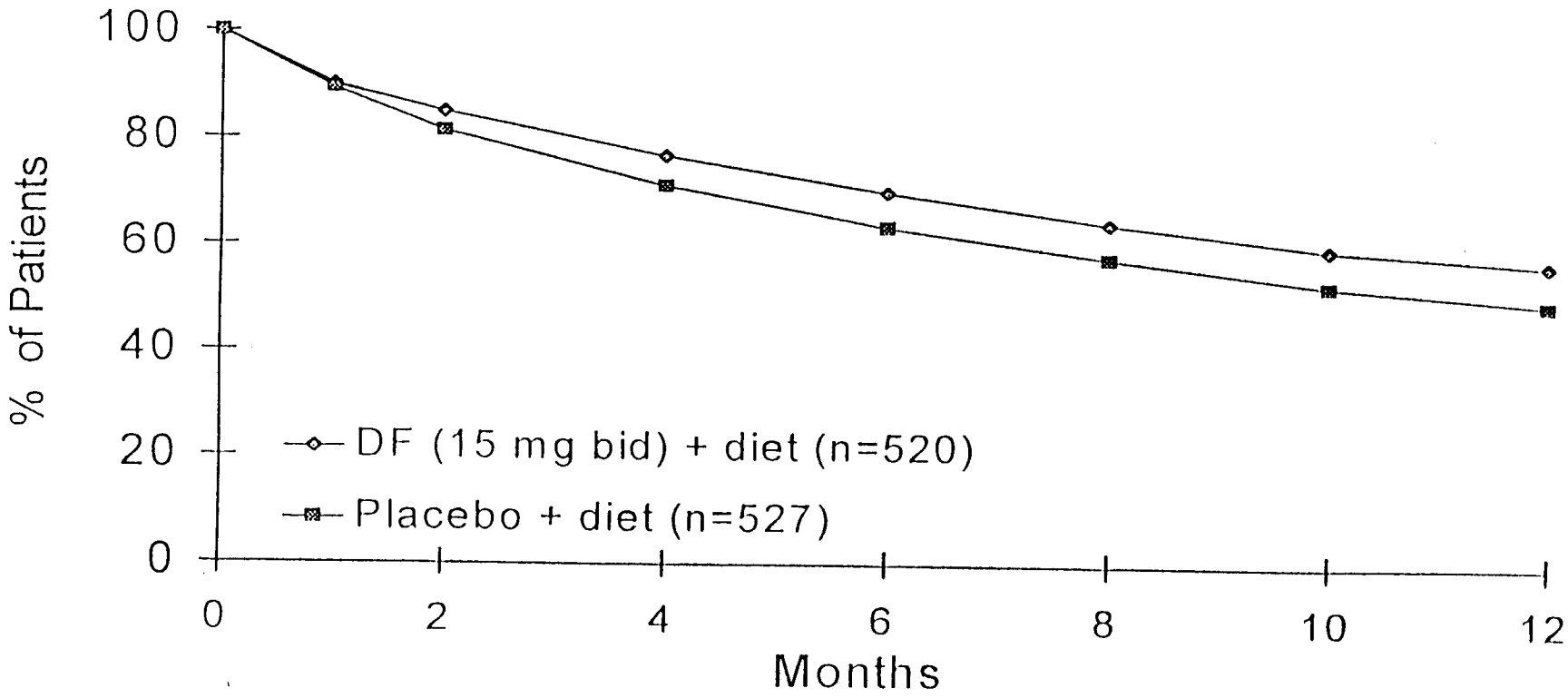


All patien

UK 18 Study:

Drug	Week	Total N	% Patients on Study
Placebo	0	22	100
	2	20	90.9
	6	19	86.3
	10	18	81.8
	14	18	81.8
	18	17	77.3
	22	17	77.3
	26	16	72.7
DF	0	23	100
	2	22	95.7
	6	22	95.7
	10	21	91.3
	14	19	82.6
	18	19	82.6
	22	18	78.3
	26	16	69.6

Percentage of Patients on Study-INDEX



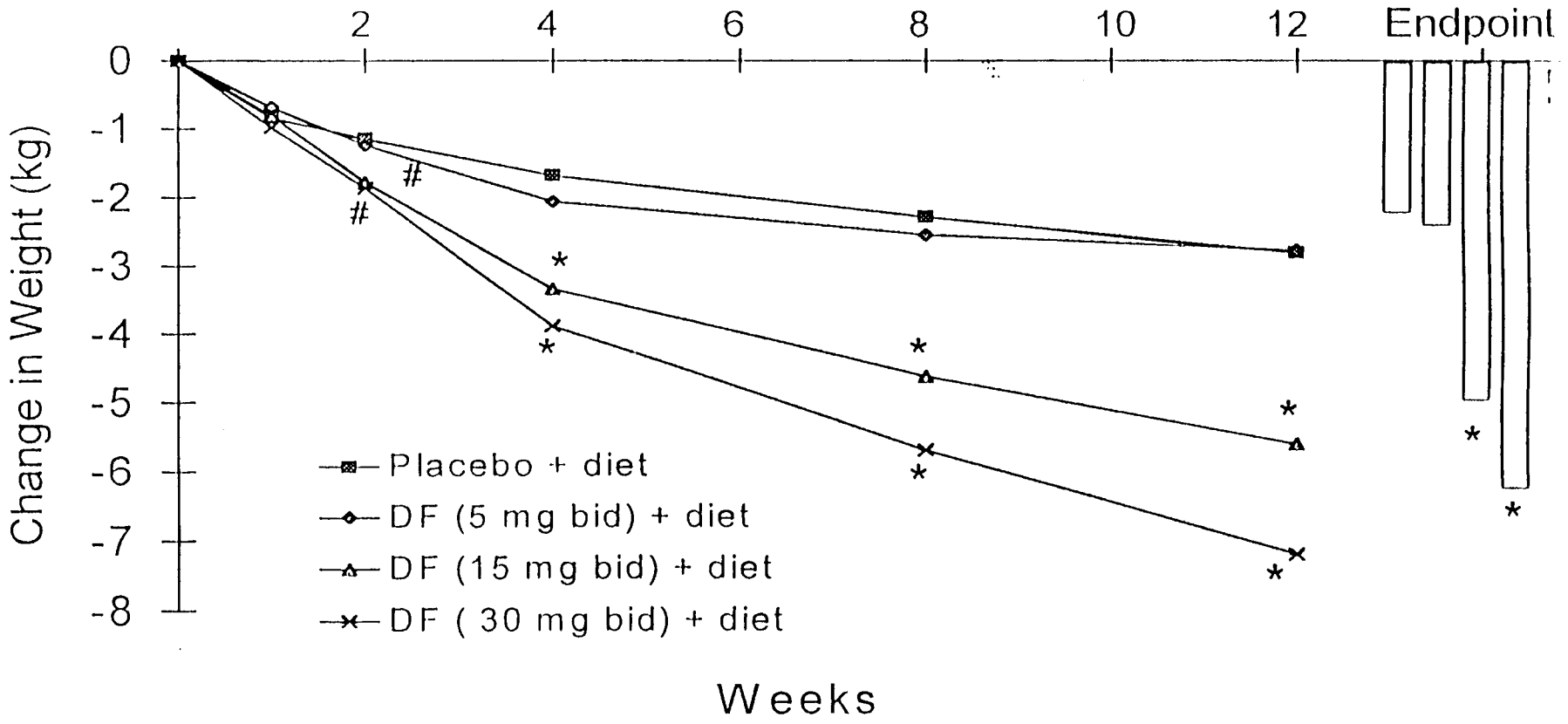
All patien

INDEX Study:

Drug	Month	Total N	% Patients on Study
Placebo	0	527	100
	1	472	89.6
	2	430	81.6
	4	377	71.5
	6	336	63.8
	8	306	58.1
	10	280	53.1
	12	262	49.7
DF	0	520	100
	1	469	90.2
	2	443	85.2
	4	401	77.1
	6	366	70.4
	8	336	64.6
	10	312	60.0
	12	298	57.3

RESPONSES SHOWN BY COMPLETERS

Dose-Response Effects of Dexfenfluramine - IP92-003



# $p < 0.04$; * $p < 0.0001$

Pbo n=82,81,77,72,62,55
DF (5) n=83,83,77,73,66,
DF (15) n=77,77,70,66,62
DF (30) n=76,76,71,64,57

Table Q. Pairwise Comparisons for Mean Absolute Weight Change from Baseline (kg) - Patients Continuing in the Study.

Week	Least Squares Adjusted Treatment Means				p-value[2]					
	P	D10	D30	D60	P v. D10	P v. D30	P v. D60	D10 v. D30	D10 v. D60	D30 v. D60
Baseline	96.81 (n=82)	94.04 (n=83)	93.94 (n=77)	93.56 (n=76)	NS	NS	NS	NS	NS	NS
1	-0.83 (n=81)	-0.68 (n=83)	-0.81 (n=77)	-0.98 (n=76)	NS	NS	NS	NS	NS	NS
2	-1.14 (n=77)	-1.24 (n=77)	-1.78 (n=70)	-1.86 (n=71)	NS	0.0140	0.0044	0.0433	0.0165	NS
4	-1.68 (n=72)	-2.07 (n=73)	-3.34 (n=66)	-3.89 (n=64)	NS	0.0001	0.0001	0.0005	0.0001	NS
8	-2.30 (n=62)	-2.56 (n=66)	-4.64 (n=62)	-5.70 (n=57)	NS	0.0001	0.0001	0.0002	0.0001	NS
12	-2.83 (n=55)	-2.79 (n=60)	-5.63 (n=57)	-7.23 (n=54)	NS	0.0003	0.0001	0.0002	0.0001	0.0379

[2]P-value associated with pooled variance t-test of the least squares means using the residual mean error from an analysis of variance model with effects for treatment, center, and their interaction.
P=placebo, D10=dexfenfluramine 10 mg, D30=dexfenfluramine 30 mg, D60=dexfenfluramine 60 mg.
NS=not significant.
Abstracted from Appendix H, Table 2B.1.

(2) Weight Change as a Percent of Initial Overweight

The analysis of weight change as a percent of initial overweight determined how much patients' weight changed in proportion to how overweight they were at baseline. Initial overweight was determined by subtracting the patients' ideal weight from their actual weight at baseline. The 1983 Metropolitan Life Insurance Company height and weight tables (mid-point of medium frame) were used to determine ideal weight.

Table P. Pairwise Comparisons for Absolute Weight Change from Baseline (kg) - Last Value Carried Forward

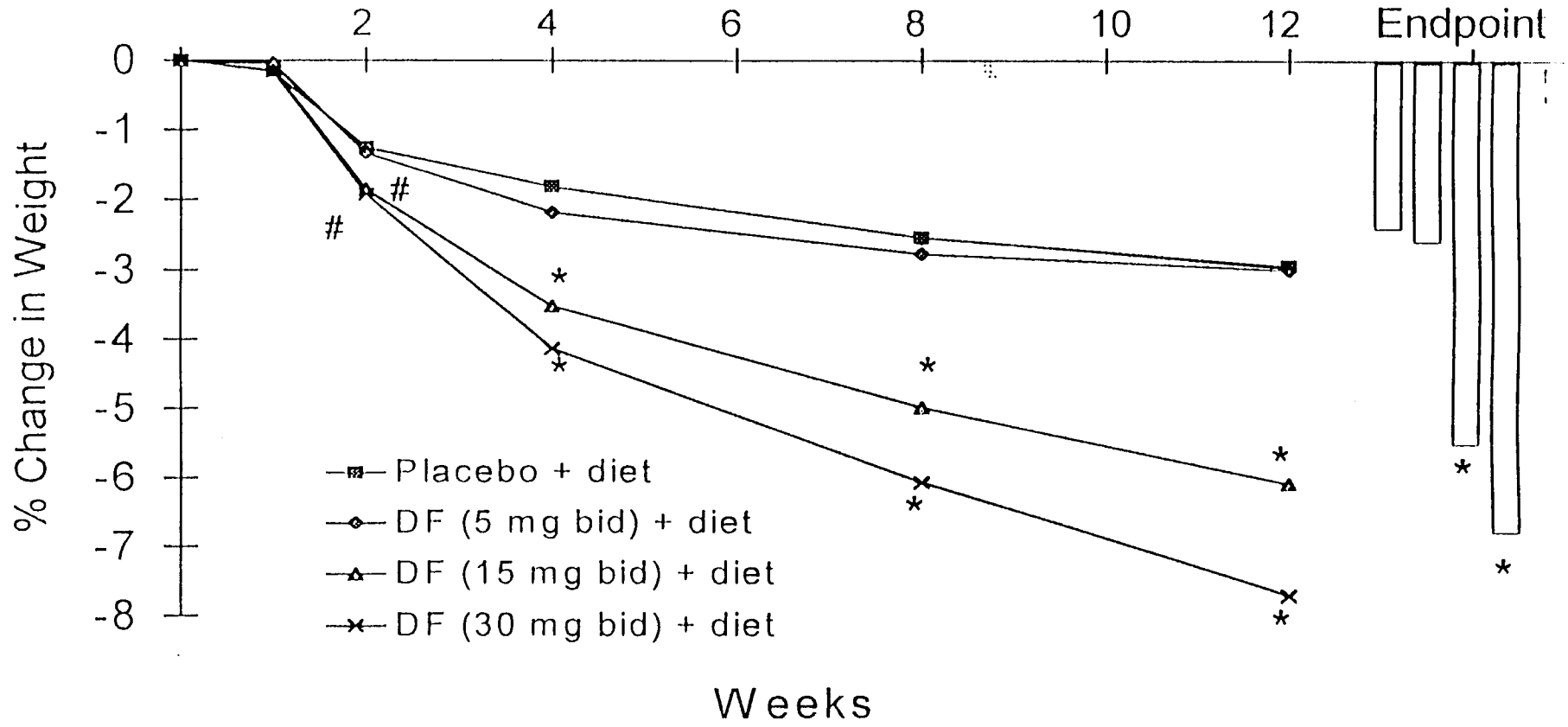
Week	Least Squares Adjusted Treatment Means				p-value[1]					
	P	D10	D30	D60	P v. D10	P v. D30	P v. D60	D10 v. D30	D10 v. D60	D30 v. D60
Baseline	96.81 (n=82)	94.04 (n=83)	93.94 (n=77)	93.56 (n=76)	NS	NS	NS	NS	NS	NS
1	-0.83 (n=81)	-0.68 (n=83)	-0.81 (n=77)	-0.98 (n=76)	NS	NS	NS	NS	NS	NS
2	-1.12 (n=80)	-1.09 (n=83)	-1.65 (n=77)	-1.78 (n=76)	NS	0.0320	0.0082	0.0241	0.0058	NS
4	-1.54 (n=81)	-1.80 (n=83)	-2.95 (n=77)	-3.43 (n=76)	NS	0.0001	0.0001	0.0007	0.0001	NS
8	-1.92 (n=80)	-2.14 (n=83)	-4.03 (n=77)	-4.74 (n=76)	NS	0.0001	0.0001	0.0001	0.0001	NS
12	-2.08 (n=81)	-2.29 (n=83)	-4.69 (n=77)	-5.75 (n=76)	NS	0.0001	0.0001	0.0001	0.0001	NS

[1]P-value associated with pooled variance t-test of the least squares means using the residual mean error from an analysis of variance model with effects for treatment, center, and their interaction.
P=placebo, D10=dexfenfluramine 10 mg, D30=dexfenfluramine 30 mg, D60=dexfenfluramine 60 mg.
NS=not significant.
Abstracted from Appendix H, Table 2B.2.

Relationship of Weight Change to Baseline Weight

An analysis of covariance model was performed using the weight change from baseline as the dependent variable (last value carried forward), with the baseline weight as the covariate. The assumptions for this analysis of covariance model were checked. The assumption test for parallelism (equal slopes for the treatment groups) was rejected at Weeks 2, 4, and 8. The slope of the lines for weight change from baseline and baseline weight was not statistically different from zero at Weeks 1 and 12. Since the statistical assumptions for the model were not achieved,

Dose-Response Effects of Dexfenfluramine - IP92-003



Pbo n=82,81,77,72,62,55
DF (5) n=83,83,77,73,66,60
DF (15) n=77,77,70,66,62,5
DF (30) n=76,76,71,64,57,4

# $p < 0.03$, * $p < 0.0001$

Table U. Pairwise Comparisons for Weight Change as a Percent of Initial Weight - Patients Continuing in the Study

Week	Least Squares Adjusted Treatment Means				p-value[1]					
	P	D10	D30	D60	P v. D10	P v. D30	P v. D60	D10 v. D30	D10 v. D60	D30 v. D60
1	-0.16 (n=81)	-0.04 (n=83)	-0.14 (n=77)	-0.16 (n=76)	NS	NS	NS	NS	NS	NS
2	-1.26 (n=77)	-1.34 (n=77)	-1.86 (n=70)	-1.94 (n=71)	NS	0.0313	0.0132	NS	0.0300	NS
4	-1.82 (n=72)	-2.19 (n=73)	-3.53 (n=66)	-4.14 (n=64)	NS	0.0001	0.0001	0.0003	0.0001	NS
8	-2.55 (n=62)	-2.78 (n=66)	-5.00 (n=62)	-6.08 (n=57)	NS	0.0001	0.0001	0.0002	0.0001	NS
12	-2.96 (n=55)	-3.01 (n=60)	-6.11 (n=57)	-7.74 (n=54)	NS	0.0001	0.0001	0.0001	0.0001	0.0442

[1]P-value associated with pooled variance t-test of the least squares means using the residual mean error from an analysis of variance model with effects for treatment, center, and their interaction.
P=placebo, D10=dexfenfluramine 10 mg, D30=dexfenfluramine 30 mg, D60=dexfenfluramine 60 mg.
NS=not significant.
Abstracted from Appendix H, Table 2A.1.

b. Post-Treatment Phase

Patients were to continue on their prescribed diets during the post-treatment phase. Weight measurements were recorded at Weeks 13, 14, 15, and 16 during the post-treatment phase. Results are presented in Tables 2A.1, 2A.2, 2B.1, 2B.2, and Figures 1 and 2, Appendix F. Individual patient data are presented in Appendix G, Data Listing 5.1. Only patients who completed the 12-week treatment phase were included in the post-treatment phase analyses.

There were no statistically significant differences among the four groups in actual weight measurements at any of the post-treatment visits.

Table T. Pairwise Comparisons for Weight Change as a Percent of Initial Weight - Last Value Carried Forward

Week	Least Squares Adjusted Treatment Means				p-value[1]					
	P	D10	D30	D60	P v. D10	P v. D30	P v. D60	D10 v. D30	D10 v. D60	D30 v. D60
1	-0.90 (n=81)	-0.74 (n=83)	-0.82 (n=77)	-1.02 (n=76)	NS	NS	NS	NS	NS	NS
2	-1.24 (n=80)	-1.18 (n=83)	-1.72 (n=77)	-1.85 (n=76)	NS	NS	0.0218	0.0365	0.0114	NS
4	-1.65 (n=81)	-1.90 (n=83)	-3.13 (n=77)	-3.65 (n=76)	NS	0.0001	0.0001	0.0005	0.0001	NS
8	-2.09 (n=80)	-2.30 (n=83)	-4.34 (n=77)	-5.04 (n=76)	NS	0.0001	0.0001	0.0001	0.0001	NS
12	-2.19 (n=81)	-2.44 (n=83)	-5.04 (n=77)	-6.12 (n=76)	NS	0.0001	0.0001	0.0001	0.0001	NS

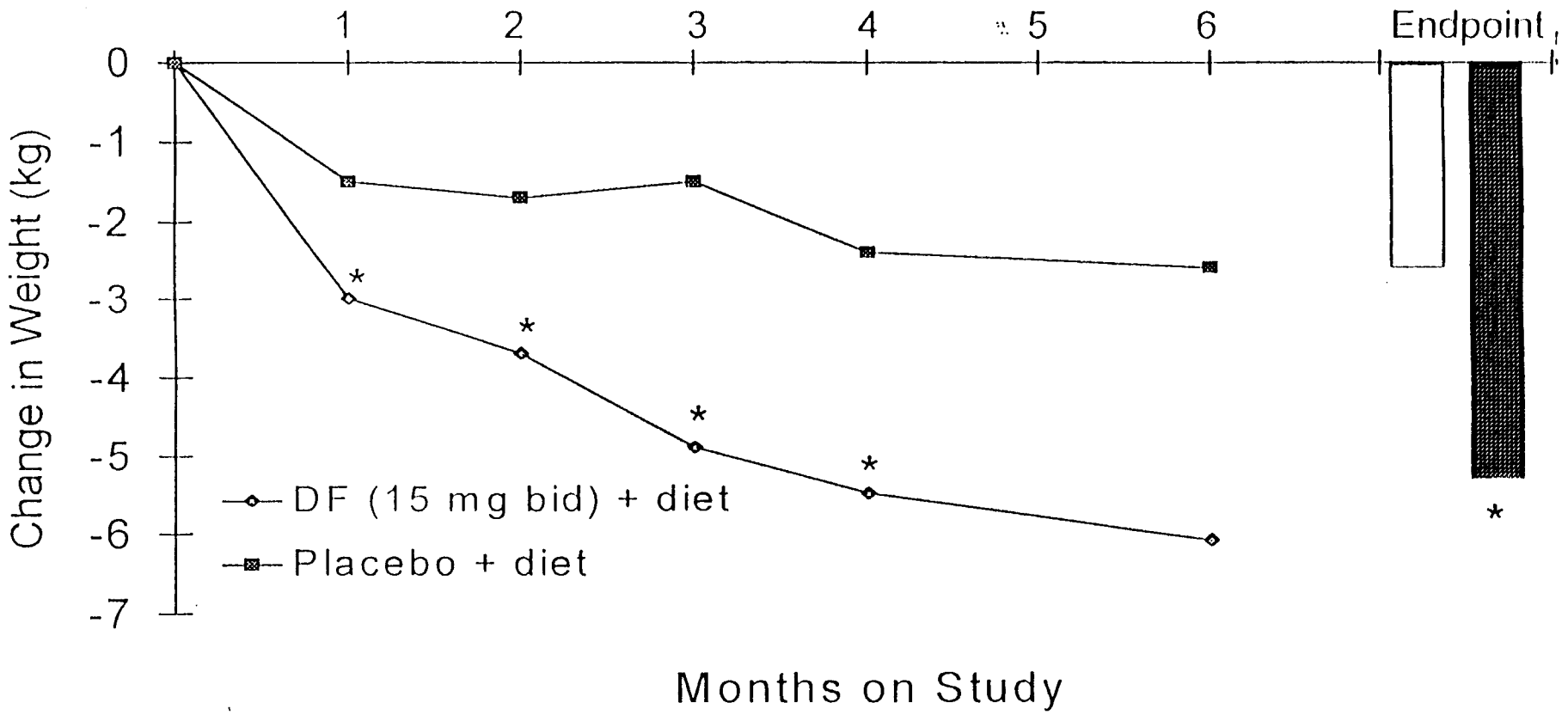
[1]P-value associated with pooled variance t-test of the least squares means using the residual mean error from an analysis of variance model with effects for treatment, center, and their interaction.
P=placebo, D10=dexfenfluramine 10 mg, D30=dexfenfluramine 30 mg, D60=dexfenfluramine 60 mg.
NS=not significant.
Abstracted from Appendix H, Table 2A.2.

Patients Continuing in the Study

As was seen in the last value carried forward analysis, there were statistically significant differences among the four treatment groups in mean weight change as a percent of initial weight from Week 2 through Week 12 for patients continuing in the study ($p \leq 0.05$). Table U, which follows, summarizes pairwise comparisons of the least squares adjusted means of weight change expressed as a percent of initial weight for patients continuing in the study.

The dexfenfluramine 60 mg group had statistically significantly greater mean weight loss as a percent of initial weight compared with the placebo group and the dexfenfluramine 10 mg group at Weeks 2, 4, 8, and 12

Effect of Dexfenfluramine vs. Placebo in Patients with Previous Weight Loss- Noble



*p<0.05

DF n=25, 23, 20, 19, 19
Placebo n=24, 24, 23, 23

patients. At Week 24, individual weight changes ranged from an increase of 2.7 kg to a decrease of 14.6 kg for dexfenfluramine patients and from an increase of 5.9 kg to a decrease of 27.3 kg for placebo patients.

Table E. Mean Absolute Weight Changes from Baseline (kg) - Patients Continuing in the Study

Visit	Treatment Group		p-value
	Dexfenfluramine Mean (±SD)	Placebo Mean (±SD)	
Baseline	93.1 (±21.6) (n=28)	99.4 (±18.1) (n=27)	0.2486
Week 1	-1.2 (±1.4) (n=28)	-0.4 (±1.4) (n=27)	0.0224
Week 2	-2.0 (±1.5) (n=27)	-1.3 (±1.3) (n=27)	0.0543
Week 4	-3.0 (±2.0) (n=25)	-1.5 (±2.1) (n=24)	0.0112
Week 8	-3.7 (±2.7) (n=23)	-1.7 (±3.2) (n=24)	0.0300
Week 12	-4.9 (±2.8) (n=20)	-1.5 (±4.9) (n=23)	0.0105
Week 16	-5.5 (±3.8) (n=19)	-2.4 (±5.4) (n=23)	0.0434
Week 24	-6.1 (±4.8) (n=19)	-2.6 (±7.2) (n=23)	0.0713

More detail on absolute weight change from baseline for patients continuing in the study can be found in Table 3B.1, Appendix H.

Table D. Mean Absolute Weight Changes from Baseline (kg) - Last Value Carried Forward

Visit	Treatment Group		p-value[1]	p-value[2]
	Dexfenfluramine (n=28) Mean (±SD)	Placebo (n=27) Mean (±SD)		
Baseline	93.1 (±21.6)	99.4 (±18.1)	0.2486	-
Week 1	-1.2 (±1.4)	-0.4 (±1.4)	0.0224	0.0163
Week 2	-2.1* (±1.5)	-1.3* (±1.3)	0.0475	0.0425
Week 4	-3.0 (±1.9)	-1.3 (±2.0)	0.0028	0.0007
Week 8	-3.6 (±2.5)	-1.6 (±3.1)	0.0101	0.0030
Week 12	-4.1 (±2.9)	-1.4 (±4.5)	0.0129	0.0015
Week 16	-4.4 (±3.7)	-2.2 (±5.0)	0.0680	0.0064
Week 24	-4.9 (±4.5)	-2.3 (±6.7)	0.1043	0.0062

* Imputing began at Week 2, using Week 1 values.

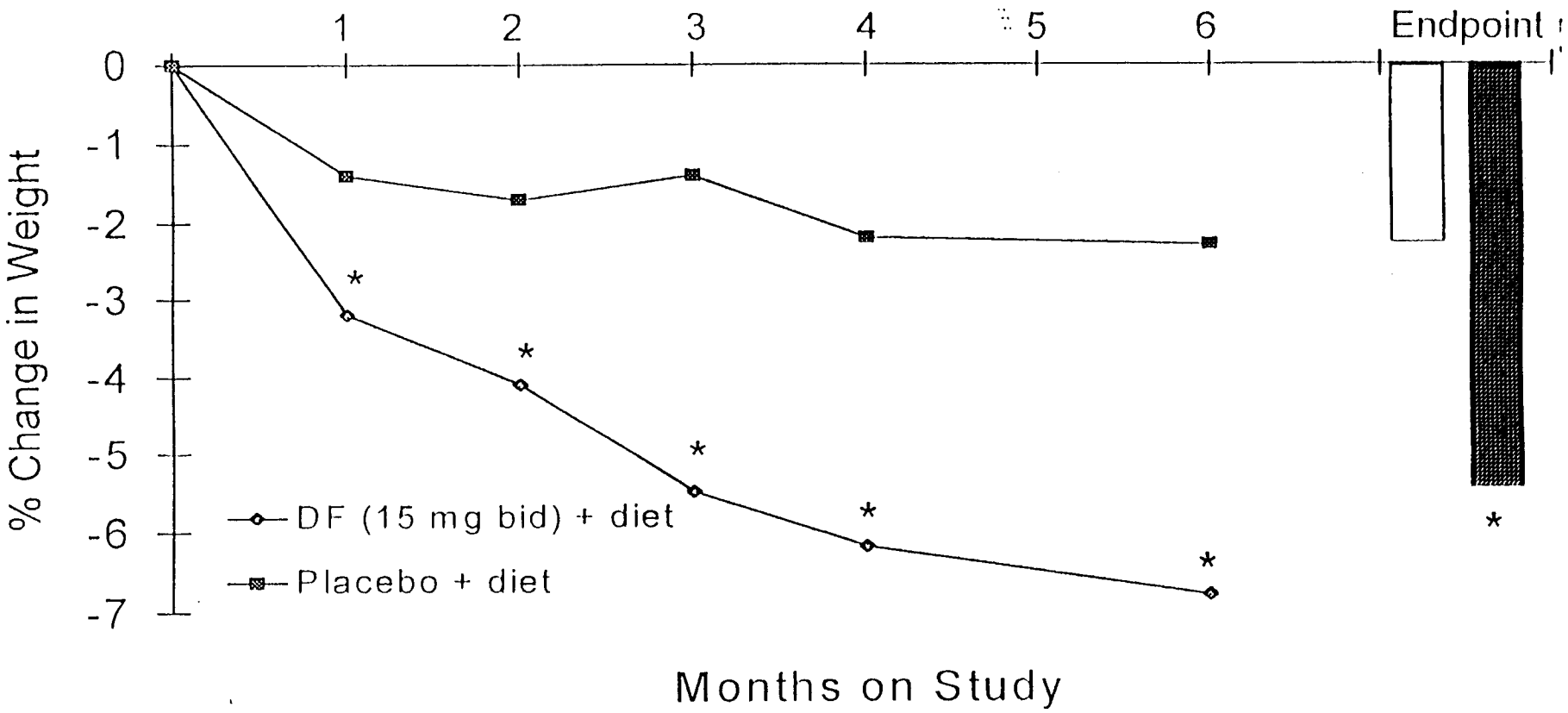
[1] P-value from an analysis of variance model with an effect for treatment; more detail can be found in Table 3B.2, Appendix H.

[2] P-value from an analysis of variance model based on ranks with an effect for treatment; more detail can be found in Table 3B.3, Appendix H.

As assessed by an analysis of variance model with an effect for treatment, dexfenfluramine patients, on the average, lost significantly more weight than their placebo counterparts at Weeks 1, 2, 4, 8, and 12, with results approaching statistical significance at Week 16 (p=0.07). Results at Week 24 were not statistically significantly different (p=0.1043). At Week 12, the mean weight change was -4.1 kg in the dexfenfluramine group and -1.4 kg in the placebo group. At Week 24, the study endpoint, the mean weight change was -4.9 kg and -2.3 kg for dexfenfluramine and placebo, respectively.

At Week 12, individual weight changes ranged from an increase of 1.4 kg to a decrease of 9.1 kg for dexfenfluramine patients and from an increase of 7.2 kg to a decrease of 16.0 kg for placebo patients. At Week 24, individual weight changes ranged from an

Effect of Dexfenfluramine vs. Placebo in Patients with Previous Weight Loss- Noble



*p<0.02

DF n=25, 23, 20, 19, 19
Placebo n=24, 24, 23, 23,

(range -2.7% to +13.8%) compared to 2.3% for placebo patients (range
-7.8% to 21.6%).

Table I. **Mean Weight Change as a Percent of Initial Weight - Patients Continuing in the Study**

Visit	Treatment Group		p-value
	Dexfenfluramine Mean (±SD)	Placebo Mean (±SD)	
Week 1	-1.4% (±1.5%) (n=28)	-0.4% (±1.4%) (n=27)	0.0115
Week 2	-2.3%* (±1.8%) (n=27)	-1.3%* (±1.4%) (n=27)	0.0228
Week 4	-3.2% (±2.0%) (n=25)	-1.4% (±1.9%) (n=24)	0.0026
Week 8	-4.1% (±2.9%) (n=23)	-1.7% (±3.0%) (n=24)	0.0077
Week 12	-5.5% (±3.2%) (n=20)	-1.4% (±4.6%) (n=23)	0.0017
Week 16	-6.2% (±4.2%) (n=19)	-2.2% (±4.7%) (n=23)	0.0073
Week 24	-6.8% (±5.1%) (n=19)	-2.3% (±6.4%) (n=23)	0.0192

* Imputing began at Week 2.
More detail on weight loss as a percent of initial weight for patients continuing in the study can be found in Table 3A.1, Appendix H.

2. Appetite and Carbohydrate Craving Evaluations

Summary data for the analyses of global appetite and carbohydrate craving evaluations are presented in Tables 4A and 4B, Appendix H. Data for individual patient scores on the visual analog scales as well as responses to the carbohydrate craving questionnaire are provided in Data Listings 8A and 8B.

lost an average of 4.6% of their initial weight , compared with 1.3% of initial weight for placebo patients. By Week 24, the corresponding mean percentage losses were 5.3% for dexfenfluramine patients and 2.1% for placebo patients. These results, including p-values for between-group comparisons, are summarized in Table H below.

Table H. Mean Weight Change as a Percent of Initial Weight - Last Value Carried Forward

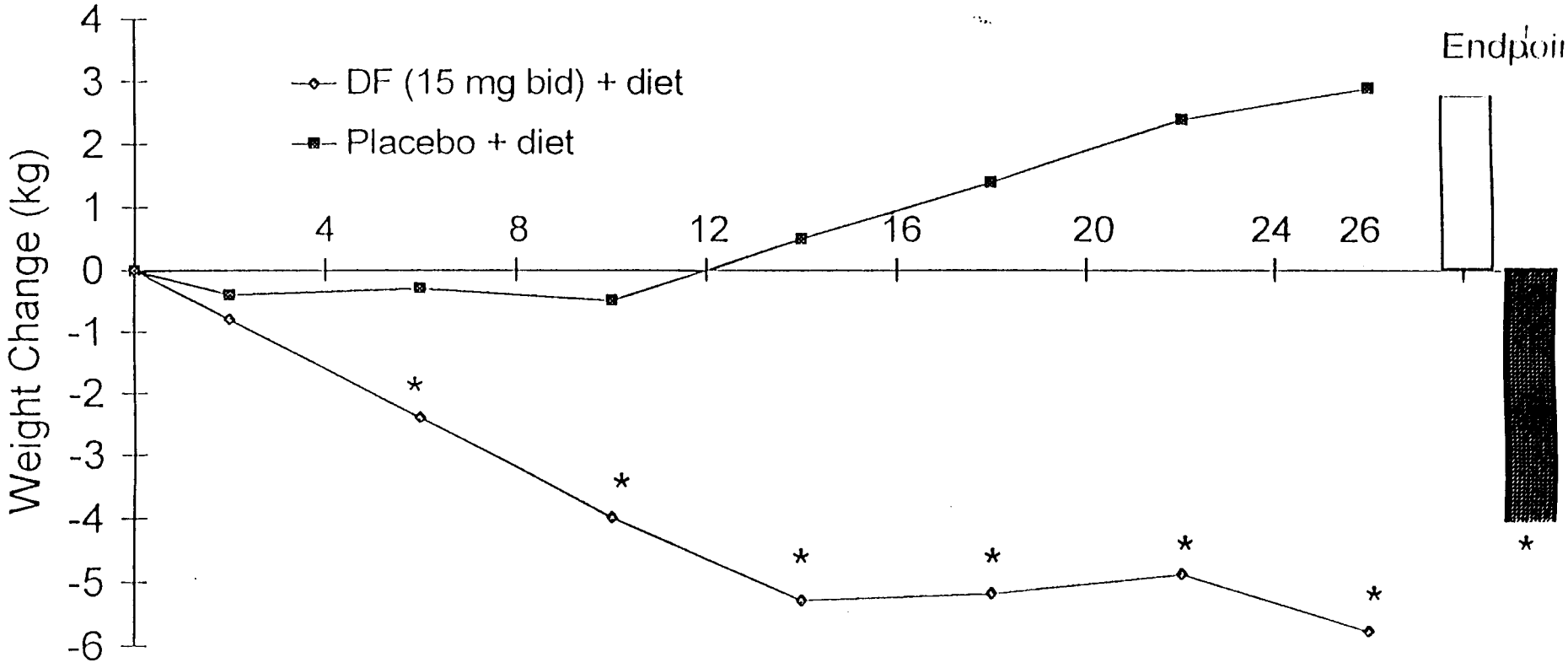
Visit	Treatment Group		p-value
	Dexfenfluramine (n=28) Mean (±SD)	Placebo (n=27) Mean (±SD)	
Week 1	-1.4% (±1.5%)	-0.4% (±1.4%)	0.0115
Week 2	-2.3% (±1.7%)	-1.3% (±1.4%)	0.0238
Week 4	-3.2% (±2.0%)	-1.3% (±1.8%)	0.0005
Week 8	-4.0% (±2.7%)	-1.6% (±2.9%)	0.0021
Week 12	-4.6% (±3.3%)	-1.3% (±4.3%)	0.0024
Week 16	-4.9% (±4.1%)	-2.1% (±4.4%)	0.0151
Week 24	-5.3% (±4.8%)	-2.1% (±6.0%)	0.0329

More detail on weight loss as a percent of initial weight using last value carried forward can be found in Table 3A.2, Appendix H.

Patients Continuing in the Study

Table I, which follows, summarizes mean weight change as a percent of initial weight using patients continuing in the study and includes p-values for between-group comparisons. Statistically significant results demonstrating greater efficacy for dexfenfluramine as compared with placebo were observed at all timepoints through Week 24 ($p \leq 0.05$). By Week 12, dexfenfluramine patients had lost 5.5% of their initial weight , while placebo patients had lost 1.4% of their initial weight By Week 24, dexfenfluramine patients had lost 6.8% of their initial weight

Effect of Dexfenfluramine vs. Placebo in Patients with Previous Weight Loss- UK 18



* $p < 0.03$

DF n=22,20,20,21,18,17,18,16
Placebo n=20, 18,19,18,15,16,14,1

Results similar to the last value carried forward analyses were seen for the analyses of patients continuing in the study. Differences between the treatment groups in mean absolute weight change from active treatment baseline were statistically significant at Weeks 6, 10, 14, 18, 22, and 26, with the dexfenfluramine group losing an average of 5.8 kg by Week 26, compared with an average weight gain of 2.9 kg for the placebo group. Weight change from active treatment baseline to Week 26 ranged from a loss of 22.4 kg to a gain of 3.7 kg for the dexfenfluramine group and from a loss of 5.9 kg to a gain of 10.1 kg for the placebo group. It should be noted that a high degree of variability was present at some timepoints.

Table F. Mean Absolute Weight Change from Active Treatment Baseline (kg) - Patients Continuing in the Study

Visit	Treatment Group		p-value
	Dexfenfluramine Mean (±SD)	Placebo Mean (±SD)	
Active Treatment Baseline	107.8 (±21.6) (n=22)	107.5 (±21.9) (n=20)	0.9737
Week 2	-0.8 (±1.9) (n=20)	-0.4 (±1.6) (n=18)	0.5047
Week 6	-2.4 (±2.9) (n=20)	-0.3 (±2.8) (n=19)	0.0318
Week 10	-4.0 (±4.5) (n=21)	-0.5 (±3.6) (n=18)	0.0102
Week 14	-5.3 (±5.5) (n=18)	0.5 (±3.8) (n=15)	0.0016
Week 18	-5.2 (±5.9) (n=17)	1.4 (±4.5) (n=16)	0.0011
Week 22	-4.9 (±6.7) (n=18)	2.4 (±4.9) (n=14)	0.0017
Week 26	-5.8 (±7.3) (n=16)	2.9 (±5.0) (n=16)	0.0004

Abstracted from Appendix G, Table 7B.1

weight gain of 2.7 kg for the placebo group. Individual patient weight change from active treatment baseline to Week 26 ranged from a loss of 22.4 kg to a gain of 6.3 kg for the dexfenfluramine group and from a loss of 5.9 kg to a gain of 10.1 kg in the placebo group. It should be noted that a high degree of variability was present for some timepoints.

Table E. Mean Absolute Weight Change from Active Treatment Baseline (kg) - Last Value Carried Forward

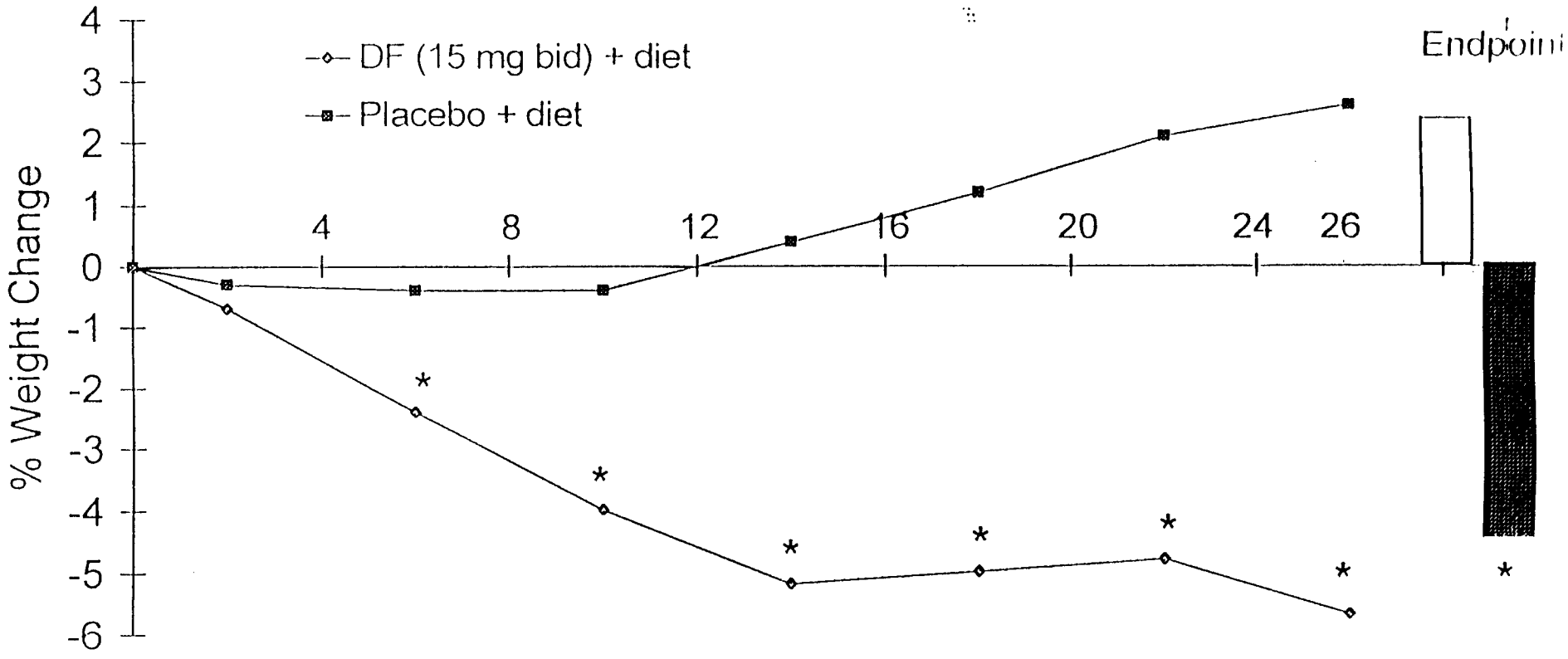
Visit	Treatment Group		p-value
	Dexfenfluramine Mean (±SD)	Placebo Mean (±SD)	
Active Treatment Baseline	107.8 (±21.6) (n=22)	107.5 (±21.9) (n=20)	0.9737
Week 2	-0.8 (±1.9) (n=20)	-0.4 (±1.6) (n=18)	0.5047
Week 6	-2.1 (±2.9) (n=22)	-0.3 (±2.8) (n=20)	0.0452
Week 10	-3.8 (±4.4) (n=22)	-0.2 (±3.6) (n=20)	0.0055
Week 14	-4.3 (±5.6) (n=22)	0.7 (±3.6) (n=20)	0.0014
Week 18	-4.3 (±5.9) (n=22)	1.5 (±4.1) (n=20)	0.0008
Week 22	-3.9 (±6.6) (n=22)	1.8 (±4.4) (n=20)	0.0021
Week 26	-4.0 (±7.2) (n=22)	2.7 (±4.6) (n=20)	0.0011

Abstracted from Appendix G, Table 7B.2

Patients Continuing in the Study

Table F, which follows, summarizes mean absolute weight changes from active treatment baseline for those patients continuing in the study. There was no statistically significant difference between treatment groups at baseline in regard to weight.

Effect of Dexfenfluramine vs. Placebo in Patients with Previous Weight Loss- UK 18



* $p < 0.03$

DF n=22,20,20,21,18,17,18,16
Placebo n=20,18,19,18,15,16,14,1

weight at Weeks 6, 10, 14, 18, 22, and 26, with the dexfenfluramine group losing an average of 4.0% of their active treatment baseline weight by Week 26, compared with an average gain of 2.3% for the placebo group. At Week 26, weight change as a percent of active treatment baseline weight ranged from a loss of 21.2% to a gain of 5.2% in the dexfenfluramine group and from an loss of 6.7% to a gain of 10.7% in the placebo group. It should be noted that a high degree of variability was present for some timepoints.

Table I. **Mean Weight Change as a Percent of Active Treatment Baseline Weight - Last Value Carried Forward**

Visit	Treatment Group		p-value
	Dexfenfluramine Mean (±SD)	Placebo Mean (±SD)	
Week 2	-0.7% (±1.8) (n=20)	-0.3% (±1.4) (n=18)	0.4493
Week 6	-2.4% (±2.8) (n=20)	-0.4% (±2.5) (n=20)	0.0240
Week 10	-3.8% (±4.3) (n=22)	-0.2% (±3.4) (n=20)	0.0046
Week 14	-4.3% (±5.4) (n=21)	+0.7% (±3.6) (n=18)	0.0019
Week 18	-4.0% (±5.6) (n=21)	+1.3% (±4.3) (n=19)	0.0018
Week 22	-3.9% (±6.3) (n=22)	+1.9% (±4.4) (n=18)	0.0023
Week 26	-4.0% (±6.8) (n=22)	+2.3% (±4.6) (n=20)	0.0014

Abstracted from Appendix G, Table 7A.2

Patients Continuing in the Study

Table J, which follows, displays mean weight change as a percent of active treatment baseline weight for patients continuing in the study.

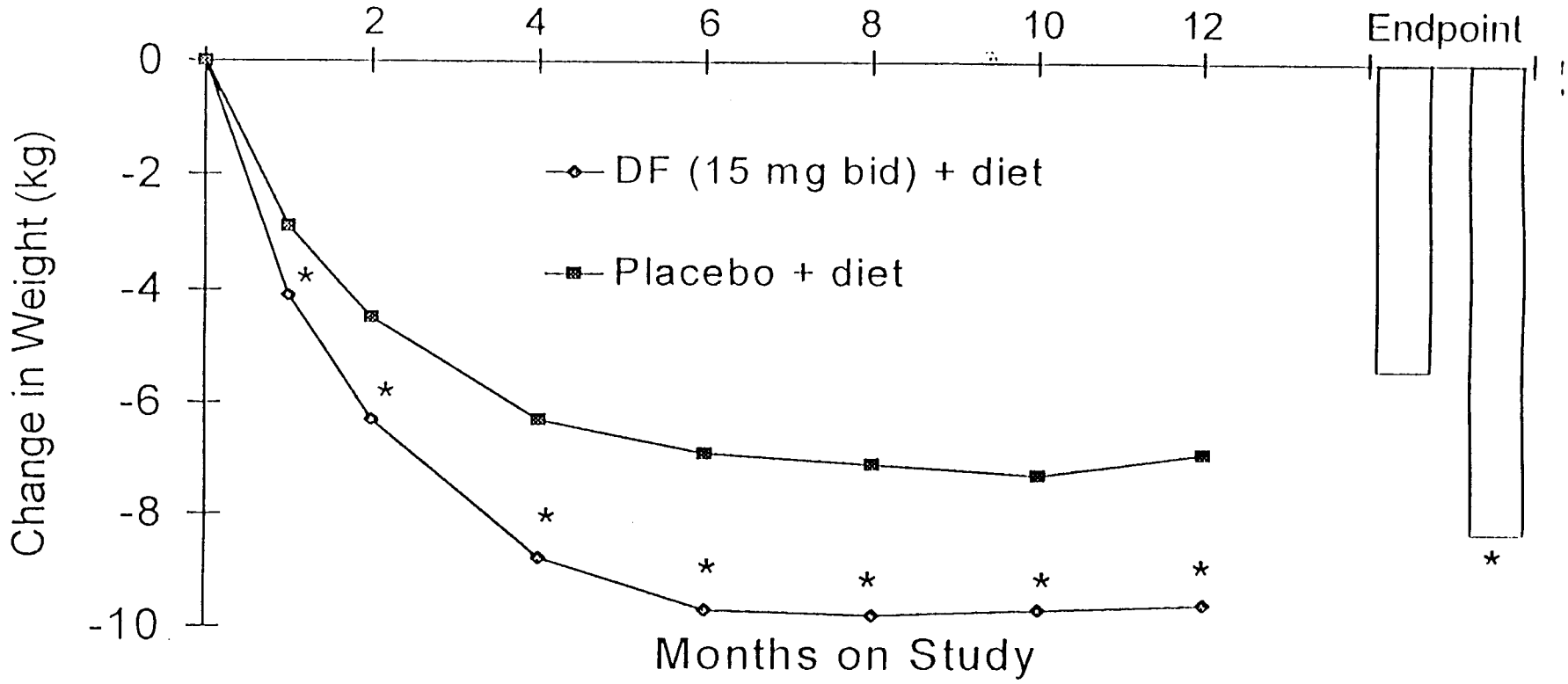
Results for patients continuing in the study were similar to the last value carried forward results. There were statistically significant differences between treatment groups for weight change as a percent of active treatment baseline weight at Weeks 6, 10, 14, 18, 22, and 26, with the dexfenfluramine group losing an average of 5.7% of their active treatment baseline weight by Week 26, compared with an average gain of 2.6% for the placebo group. At Week 26, weight change as a percent of active treatment baseline weight ranged from a loss of 21.2% to a gain of 4.0% in the dexfenfluramine group and from an loss of 6.7% to a gain of 10.7% in the placebo group. It should be noted that a high degree of variability was present for some timepoints for the placebo group.

Table J. **Mean Weight Change as a Percent of Active Treatment Baseline Weight - Patients Continuing in the Study**

Visit	Treatment Group		p-value
	Dexfenfluramine Mean (±SD)	Placebo Mean (±SD)	
Week 2	-0.7% (±1.8) (n=20)	-0.3% (±1.4) (n=18)	0.4493
Week 6	-2.4% (±2.8) (n=20)	-0.4% (±2.6) (n=19)	0.0280
Week 10	-4.0% (±4.3) (n=21)	-0.4% (±3.4) (n=18)	0.0080
Week 14	-5.2% (±5.3) (n=18)	+0.4% (±3.8) (n=15)	0.0019
Week 18	-5.0% (±5.7) (n=17)	+1.2% (±4.6) (n=16)	0.0015
Week 22	-4.8% (±6.5) (n=18)	+2.1% (±4.9) (n=14)	0.0023
Week 26	-5.7% (±7.0) (n=16)	+2.6% (±5.0) (n=16)	0.0005

Abstracted from Appendix G, Table 7A.1

Effect of Dexfenfluramine vs. Placebo - INDEX



*p<0.0002

DF n = (469), 463, 440, 396, 359, 326, 309, 297
Placebo n = (472) 466, 424, 375, 333, 297, 276, 26

Table L. Mean Absolute Weight Changes from Baseline (kg) - Patients Continuing in Study

Timepoint	Treatment Group		p-value
	Dexfenfluramine mean(±SD)	Placebo mean(±SD)	
Baseline	96.8 (±19.6) n=469	97.4 (±18.7) n=472	0.6505
Month 1	-4.1 (±3.0) n=463	-2.9 (±2.7) n=466	≤0.0001
Month 2	-6.3 (±4.2) n=440	-4.5 (±4.2) n=424	≤0.0001
Month 4	-8.8 (±5.7) n=396	-6.3 (±5.9) n=375	≤0.0001
Month 6	-9.7 (±6.3) n=359	-6.9 (±6.8) n=333	≤0.0001
Month 8	-9.8 (±6.6) n=326	-7.1 (±7.3) n=297	≤0.0001
Month 10	-9.7 (±7.1) n=309	-7.3 (±7.7) n=276	≤0.0001
Month 12	-9.6 (±7.7) n=297	-6.9 (±8.0) n=262	0.0002

Absuracted from Tables 2.1 and 4.1, Appendix F.

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By Month 6, dexfenfluramine patients in Stratum W lost an average of 10.1% of their initial weight compared with an average loss of 4.9% for placebo patients. Dexfenfluramine patients in Stratum Z lost an average of 9.2% of their initial weight compared with an average loss of 6.6% for placebo patients.

By Month 12, dexfenfluramine patients in Stratum W lost an average of 9.6% of their initial weight as compared with an average loss of 4.3% for placebo patients. The corresponding average percent losses for Stratum Z were 8.8% and 6.3% for dexfenfluramine and placebo patients, respectively.

Table X.1 **Mean Weight Change as a Percent of Initial Weight by Treatment Group - Least Squares Means - Last Value Carried Forward**

Timepoint	Mean Weight Change as Percent of Initial Weight by Treatment Least Squares Means		p-value
	Dexfenfluramine	Placebo	
Month 1	-4.2	-3.0	≤0.0001
Month 2	-6.3	-4.3	≤0.0001

Abstracted from Table 3.1, Appendix F.

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Table X.2 Mean Weight Change as a Percent of Initial Weight by Treatment Group - Least Squares Means Adjusted by Stratum - Last Value Carried Forward

Timepoint	Stratum	Mean Weight Change as Percent of Initial Weight by Treatment - Least Squares Means Adjusted by Stratum		p-value[1] by Stratum
		Dexfenfluramine	Placebo	
Month 4	W	-9.4	-4.7	0.0001
	Z	-8.5	-6.2	0.0001
Month 6	W	-10.1	-4.9	0.0001
	Z	-9.2	-6.6	0.0001
Month 8	W	-9.9	-4.7	0.0001
	Z	-9.2	-6.6	0.0001
Month 10	W	-9.7	-4.2	0.0001
	Z	-9.0	-6.5	0.0001
Month 12	W	-9.6	-4.3	0.0001
	Z	-8.8	-6.3	0.0001

[1] P-value for treatment effect from a comparison of treatment groups within each stratum using the residual mean error from an analysis of variance model with effects for treatment, country, stratum, and their interactions. Abstracted from Table 3.1, Appendix G.

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Table Y.1 Mean Weight Change as a Percent of Initial Weight by Treatment Group - Least Squares Means - Patients Continuing in Study

Timepoint	Mean Weight Change as Percent of Initial Weight by Treatment - Least Squares Means		p-value
	Dexfenfluramine	Placebo	
Month 1	-4.2	-3.0	≤0.0001
Month 2	-6.5	-4.6	≤0.0001
Month 8	-10.3	-7.1	≤0.0001
Month 12	-10.1	-6.9	≤0.0001

Table Y.2 Mean Weight Change as a Percent of Initial Weight by Treatment Group - Least Squares Means Adjusted by Stratum - Patients Continuing in Study

Timepoint	Stratum	Mean Weight Change as Percent of Initial Weight by Treatment - Least Squares Means Adjusted by Stratum		p-value[1] by Stratum
		Dexfenfluramine	Placebo	
Month 4	W	-9.6	-4.9	0.0001
	Z	-9.1	-6.8	0.0001
Month 6	W	-10.8	-5.7	0.0001
	Z	-10.1	-7.3	0.0001
Month 10	W	-10.6	-5.3	0.0001
	Z	-10.4	-7.8	0.0005

[1] P-value for treatment effect from a comparison of treatment groups within each stratum using the residual mean error from an analysis of variance model with effects for treatment, country, stratum, and their interactions. Abstracted from Table 2.1, Appendix G.

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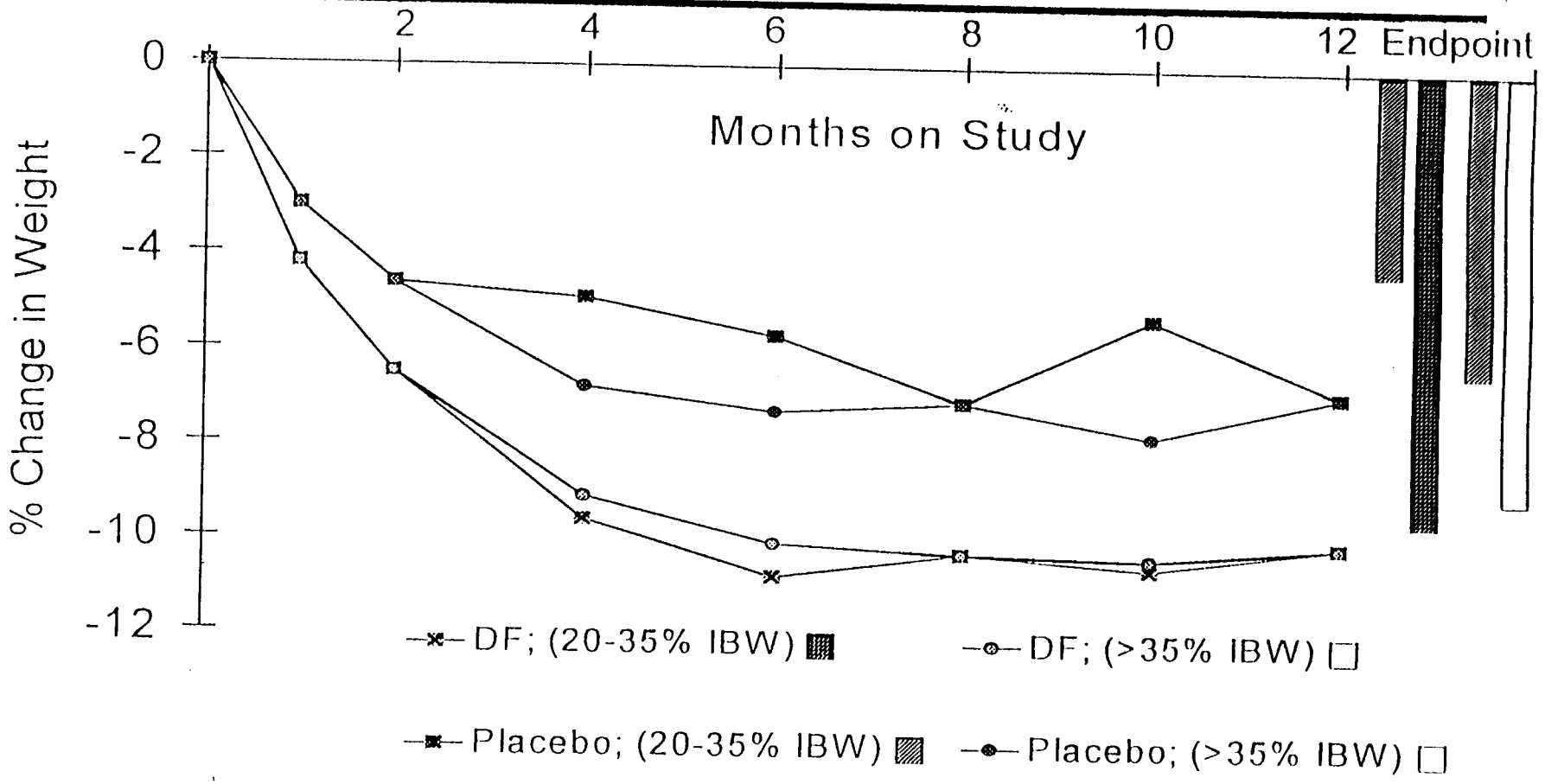
Effect of Dexfenfluramine vs. Placebo by Body Weight Stratum- INDEX



$p < 0.005$ between treatment groups within each stratum at all time points

DF n = (469), 463, 440, 396, 359, 326, 309, 297
Placebo n = (472) 466, 424, 375, 333, 297, 276, [illegible]

Table K.1 **Mean Absolute Weight Changes from Baseline (kg) - Last Value Carried Forward**

Timepoint	Treatment Group		p-value
	Dexfenfluramine mean(±SD)	Placebo mean(±SD)	
Baseline	96.8 (±19.6) n=469	97.4 (±18.7) n=472	0.6505
Month 1	-4.1 (±3.0) n=463	-2.9 (±2.7) n=466	≤0.0001
Month 2	-6.1 (±4.2) n=463	-4.3 (±4.2) n=464	≤0.0001
Month 4	-8.0 (±5.8) n=461	-5.5 (±5.8) n=465	≤0.0001
Month 6	-8.7 (±6.4) n=460	-5.8 (±6.5) n=467	≤0.0001
Month 8	-8.5 (±6.6) n=456	-5.8 (±6.9) n=462	≤0.0001
Month 10	-8.4 (±6.9) n=461	-5.7 (±7.0) n=464	≤0.0001
Endpoint[1]	-8.3 (±7.3) n=463	-5.4 (±7.1) n=467	≤0.0001

[1] Using last value carried forward at Month 12.
Abstracted from Tables 2.1 and 5A, Appendix F.

The 95% confidence interval (CI) around the least squares means at each timepoint indicated that the width of the confidence intervals increased over time, with a similar pattern for both treatment groups. These results are summarized in Table K.2, which follows.

At Month 4, the least squares adjusted mean weight reduction for dexfenfluramine patients was 7.9 kg (CI -8.4 kg, -7.4 kg) compared to a 5.0 kg reduction for placebo patients (CI -5.5 kg, -4.5 kg). At Month 6, the least squares adjusted mean weight reduction for dexfenfluramine patients was 8.6 kg (CI -9.1 kg, -8.0 kg) compared to a 5.3 kg reduction for placebo patients (CI -5.8 kg, -4.7 kg). By Month 12 (last value carried forward), the least squares adjusted mean weight reduction for

dexfenfluramine patients was 8.2 kg (CI -8.8 kg, -7.5 kg) compared to a 4.8 kg reduction for placebo patients (CI -5.5 kg, -4.2 kg). The least squares adjusted mean weight reductions for both treatments were slightly lower at all timepoints than the mean weight reductions, using last value carried forward. The maximum difference between the least squares means and the means was ≤ 0.2 kg for dexfenfluramine patients, and ≤ 0.6 kg for placebo patients.

Table K.2 **Mean Absolute Weight Changes from Baseline (kg) - Last Value Carried Forward - Stratum Effect from an Analysis of Variance Model with Effects for Country, Stratum, and their Interactions - Least Squares Means with 95% Confidence Interval**

Timepoint	Treatment Group				p-value
	Dexfenfluramine		Placebo		
	Least Squares Means	95% Confidence Interval	Least Squares Means	95% Confidence Interval	
Month 1	-3.9 n=463	-4.2,-3.7	-2.8 n=466	-3.0,-2.5	≤0.0001
Month 2	-6.0 n=463	-6.3,-5.6	-4.0 n=464	-4.4,-3.6	≤0.0001
Month 4	-7.9 n=461	-8.4,-7.4	-5.0 n=465	-5.5,-4.5	≤0.0001
Month 6	-8.6 n=460	-9.1,-8.0	-5.3 n=467	-5.8,-4.7	≤0.0001
Month 8	-8.5 n=456	-9.0,-7.9	-5.2 n=462	-5.8,-4.6	≤0.0001
Month 10	-8.3 n=461	-8.9,-7.7	-4.9 n=464	-5.6,-4.3	≤0.0001
Endpoint[1]	-8.2 n=463	-8.8,-7.5	-4.8 n=467	-5.5,-4.2	≤0.0001

[1] Using last value carried forward at Month 12.
Abstracted from Table 5A, Appendix G.

Dexfenfluramine patients in both strata had greater mean reductions than placebo patients in the corresponding stratum at all timepoints. On the average, patients in Stratum Z (patients greater than 135% of ideal weight)

had greater weight reductions than patients in Stratum W (patients 120% to 135% of ideal weight). These results are summarized in Table K.3 below.

Table K.3 **Mean Absolute Weight Changes from Baseline (kg) - Last Value Carried Forward - Least Squares Means by Treatment Group by Stratum**

Timepoint	Treatment Group	Least Squares Means (kg)		p-value[1]
		W	Z	
Baseline	Dexfenfluramine	77.6	101.2	--
	Placebo	78.2	101.2	--
	All	77.9	101.2	--
Month 1	Dexfenfluramine	-3.4	-4.4	--
	Placebo	-2.3	-3.2	--
	All	-2.9	-3.8	0.0001
Month 2	Dexfenfluramine	-5.3	-6.7	--
	Placebo	-3.2	-4.8	--
	All	-4.2	-5.7	0.0001
Month 4	Dexfenfluramine	-7.3	-8.6	--
	Placebo	-3.6	-6.3	--
	All	-5.5	-7.5	0.0001
Month 6	Dexfenfluramine	-7.8	-9.3	--
	Placebo	-3.8	-6.7	--
	All	-5.8	-8.0	0.0001
Month 8	Dexfenfluramine	-7.7	-9.2	--
	Placebo	-3.6	-6.8	--
	All	-5.7	-8.0	0.0001
Month 10	Dexfenfluramine	-7.6	-9.0	--
	Placebo	-3.25	-6.6	--
	All	-5.4	-7.8	0.0001
Endpoint[2]	Dexfenfluramine	-7.4	-8.9	--
	Placebo	-3.3	-6.3	--
	All	-5.4	-7.6	0.0005

[1] P-value for a stratum effect from an analysis of variance model with effects for country, stratum, and their interactions.
[2] Using last value carried forward at Month 12.
Abstracted from Table 5A, Appendix G.