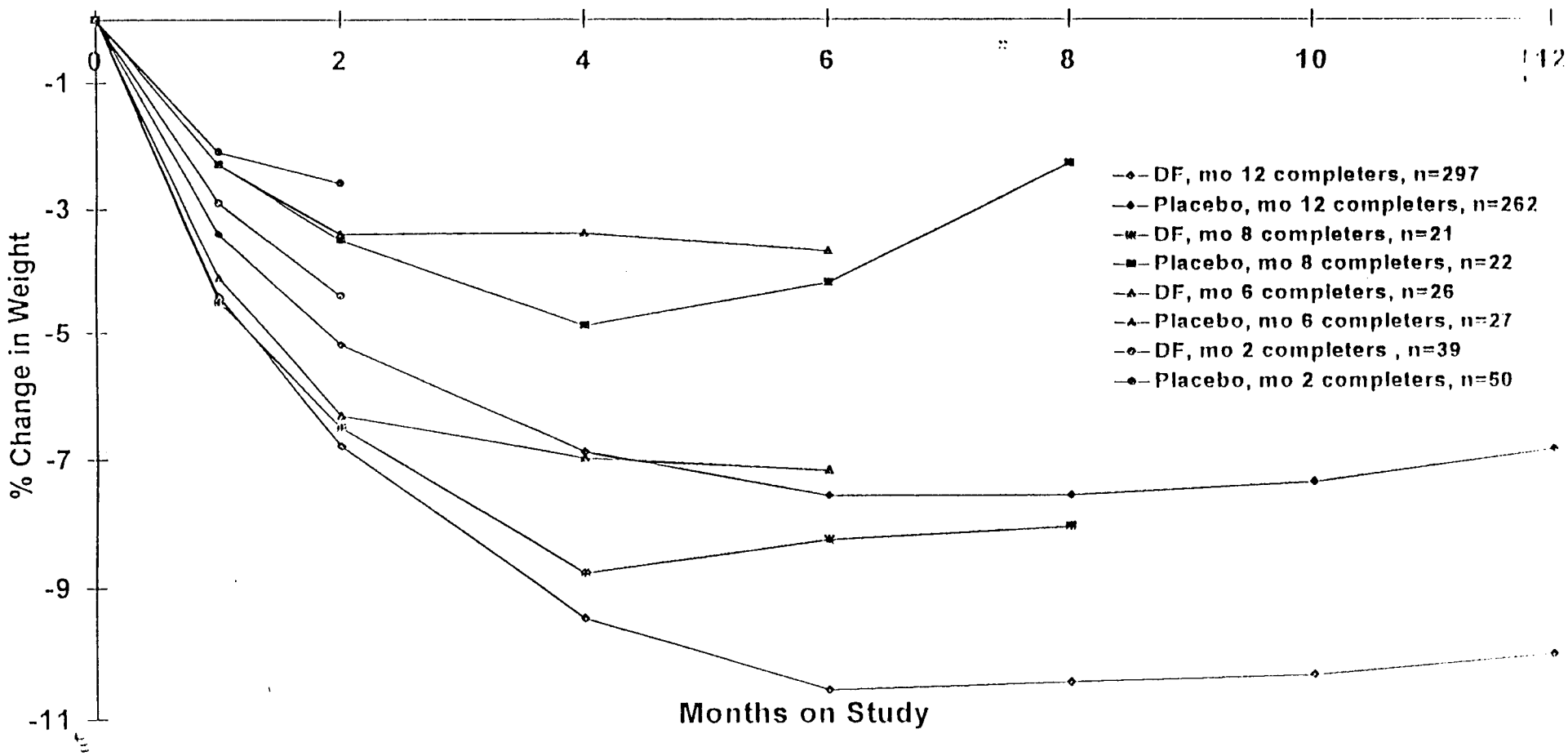
INDEX STUDY
RESPONSES OF DIFFERENT
COMPLETER GROUPS

Effect of Dexfenfluramine vs. Placebo on Different Completer Groups - INDEX



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pages of trade secret and/or confidential commercial information

TWO-TIERED ERROR BAR PLOTS

TREATMENT EFFECT DIFFERENCES BY STUDY AND TREATMENT EFFECTS BY STUDY

Treatment Effect Differences by Study
UK 18, P003, Noble and Index Studies

UK 18, PBO n=20/DF n=22

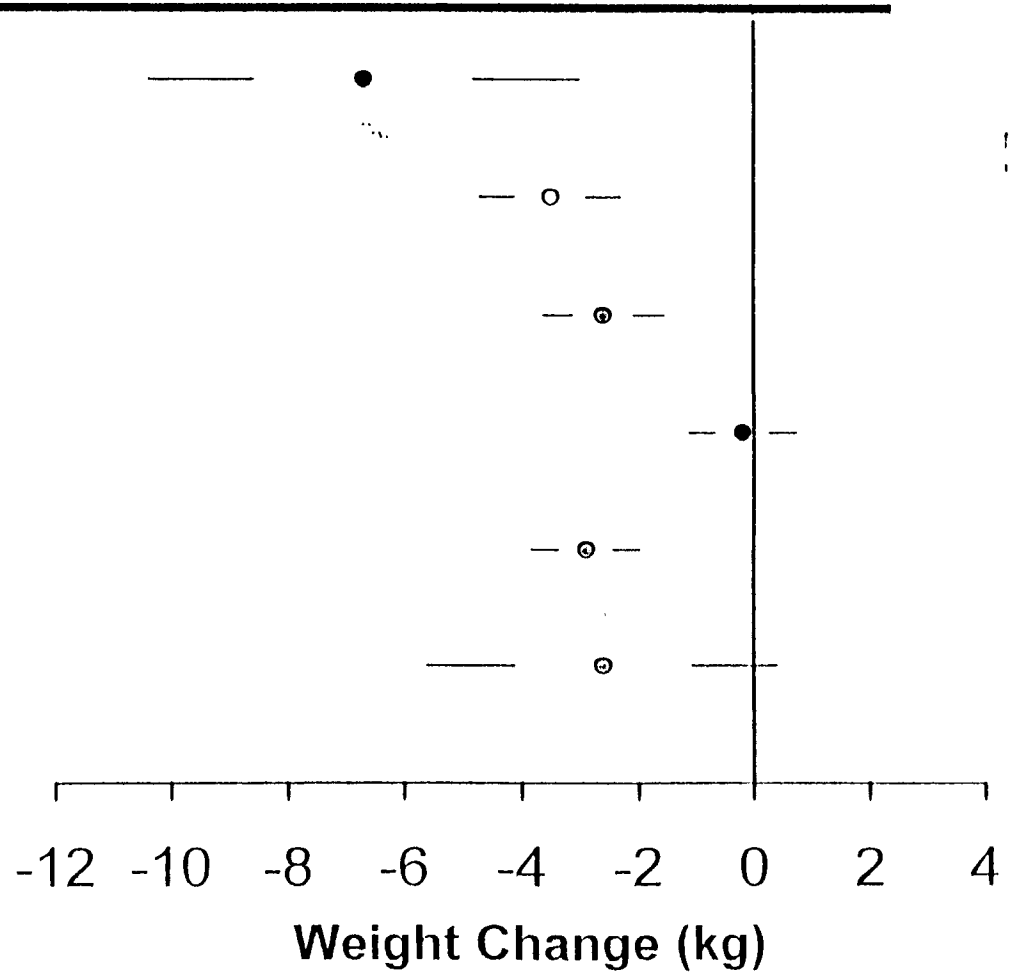
P003, PBO n=81 /60 mg DF n=76

P003, PBO n=81/ 30 mg DFn=77

P003, PBO n=81/ 10 mg DFn=83

Noble, PBO n=27/DF n=28

Index, PBO n=467/DF n=463



Treatment Effect by Study
UK 18, P003, Noble and Index Studies

Index DF n=463, PBO n=467

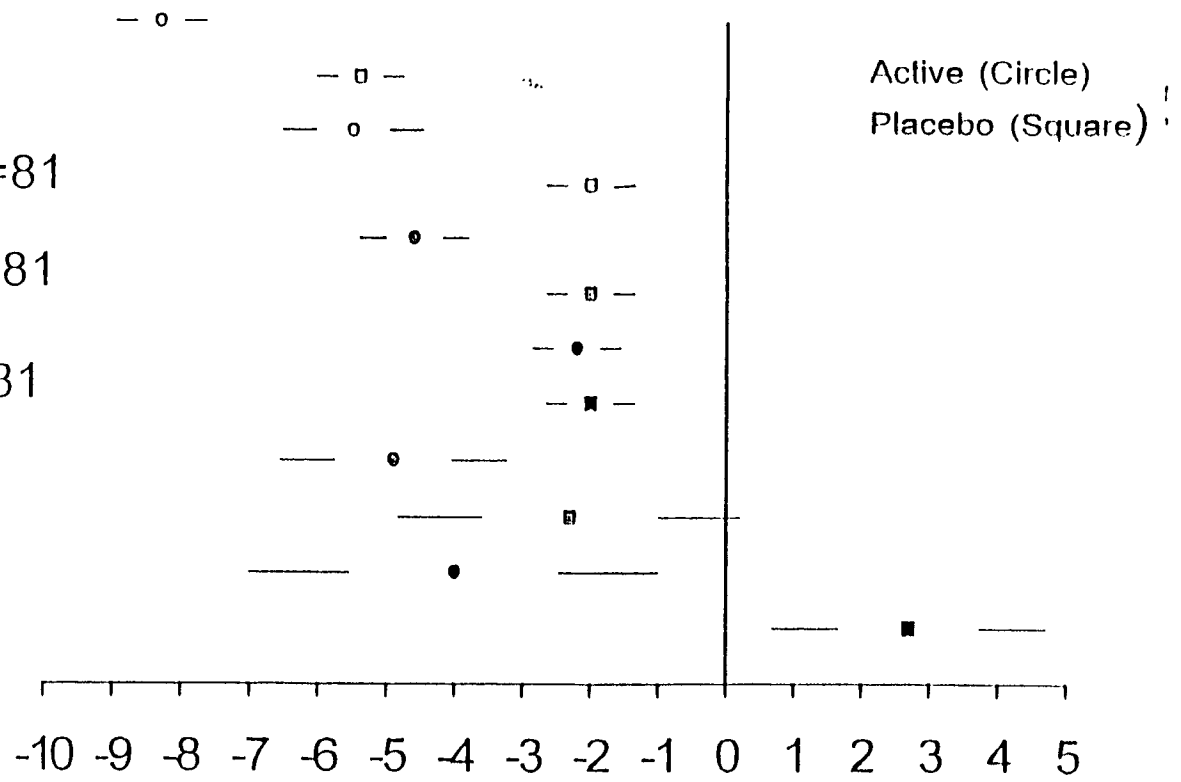
P003 60 mg DF n=76, PBO n=81

P003 30 mg DF n=77, PBO n=81

P003 10 mg DFn=83, PBO n=81

Noble DF n=28, PBO n=27

UK 18 DF n=22, PBO n=20



Treatment Effect Differences by Study
UK 18, P003, Noble and Index Studies

UK 18, PBO n=20/DF n=22

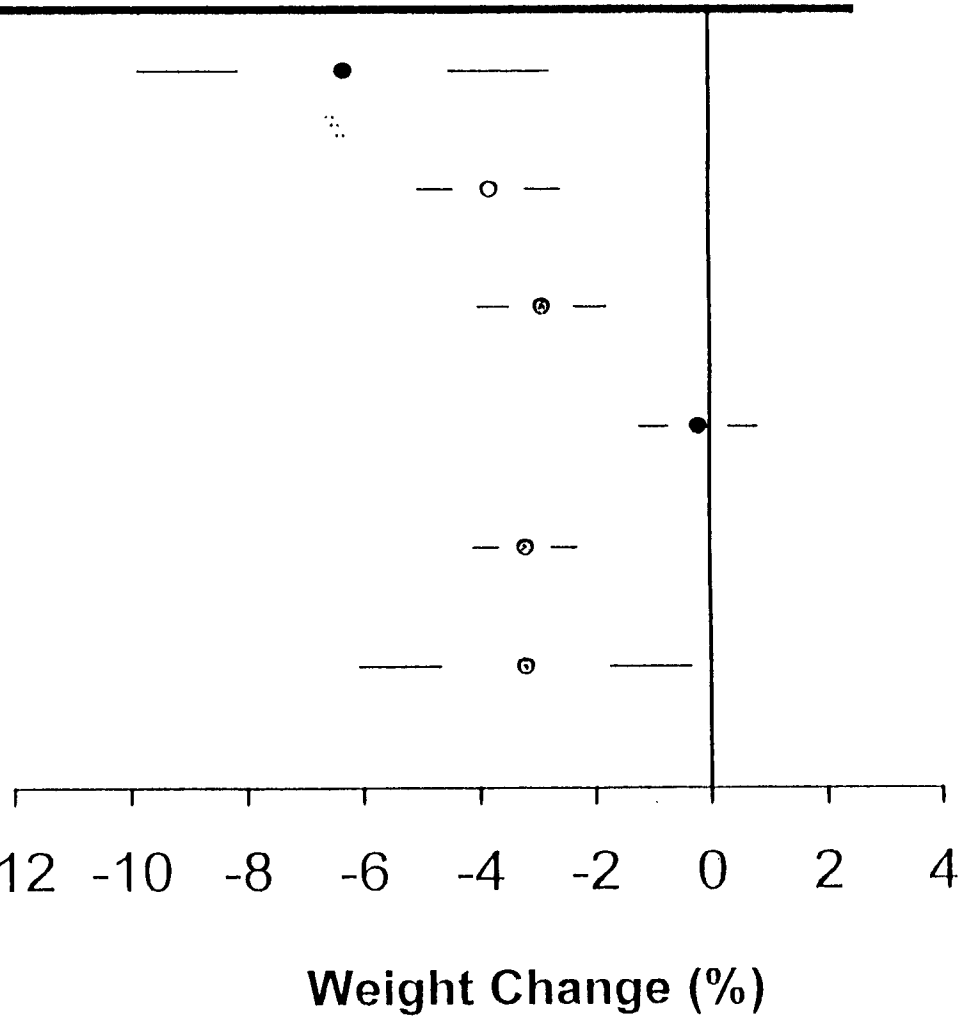
P003, PBO n=81 /60 mg DF n=76

P003, PBO n=81/ 30 mg DFn=77

P003, PBO n=81/ 10 mg DFn=83

Noble, PBO n=27/DF n=28

Index, PBO n=467/DF n=463



Treatment Effect by Study
UK 18, P003, Noble and Index Studies

Index DF n=463, PBO n=467

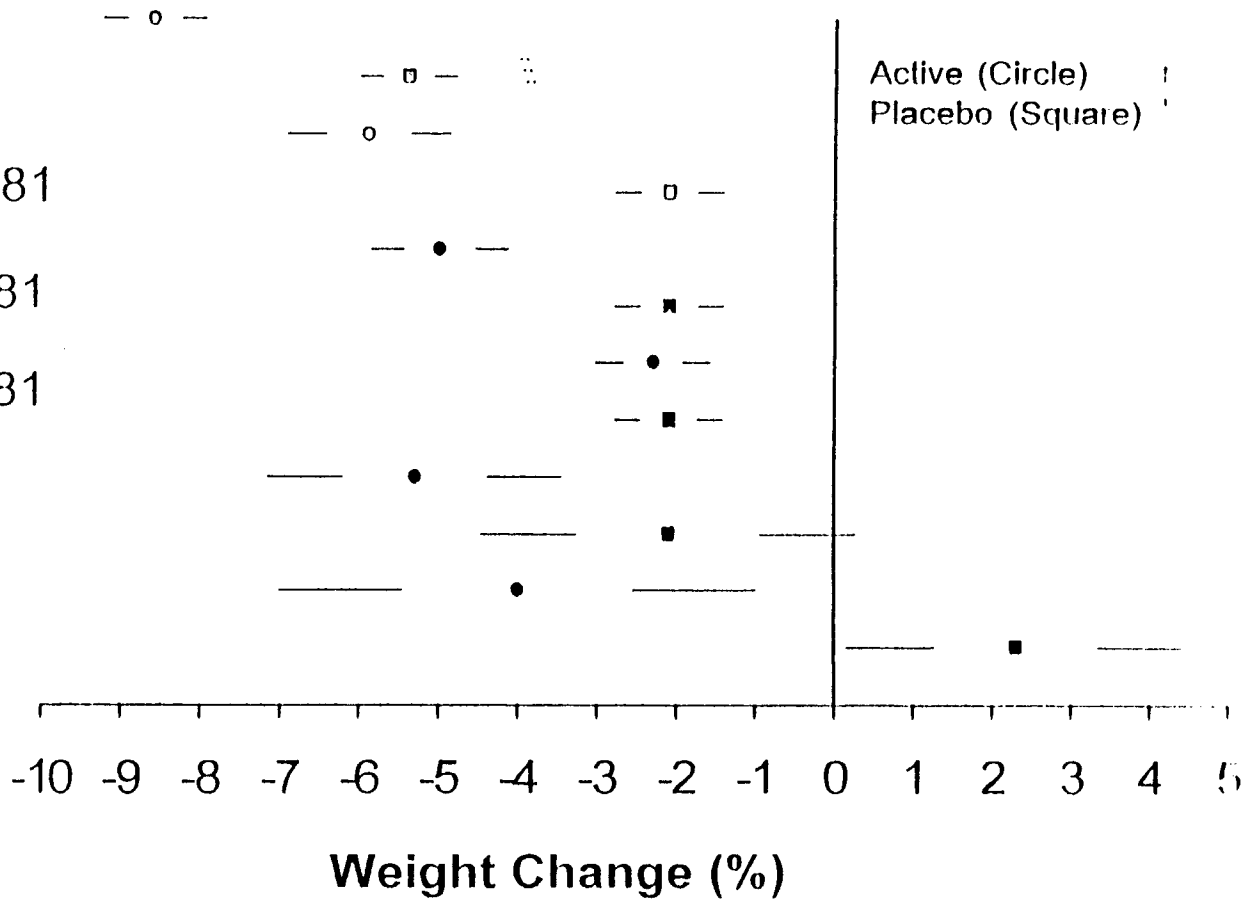
P003 60 mg DF n=76, PBO n=81

P003 30 mg DF n=77, PBO n=81

P003 10 mg DF n=83, PBO n=81

Noble DF n=28, PBO n=27

UK 18 DF n=22, PBO n=20



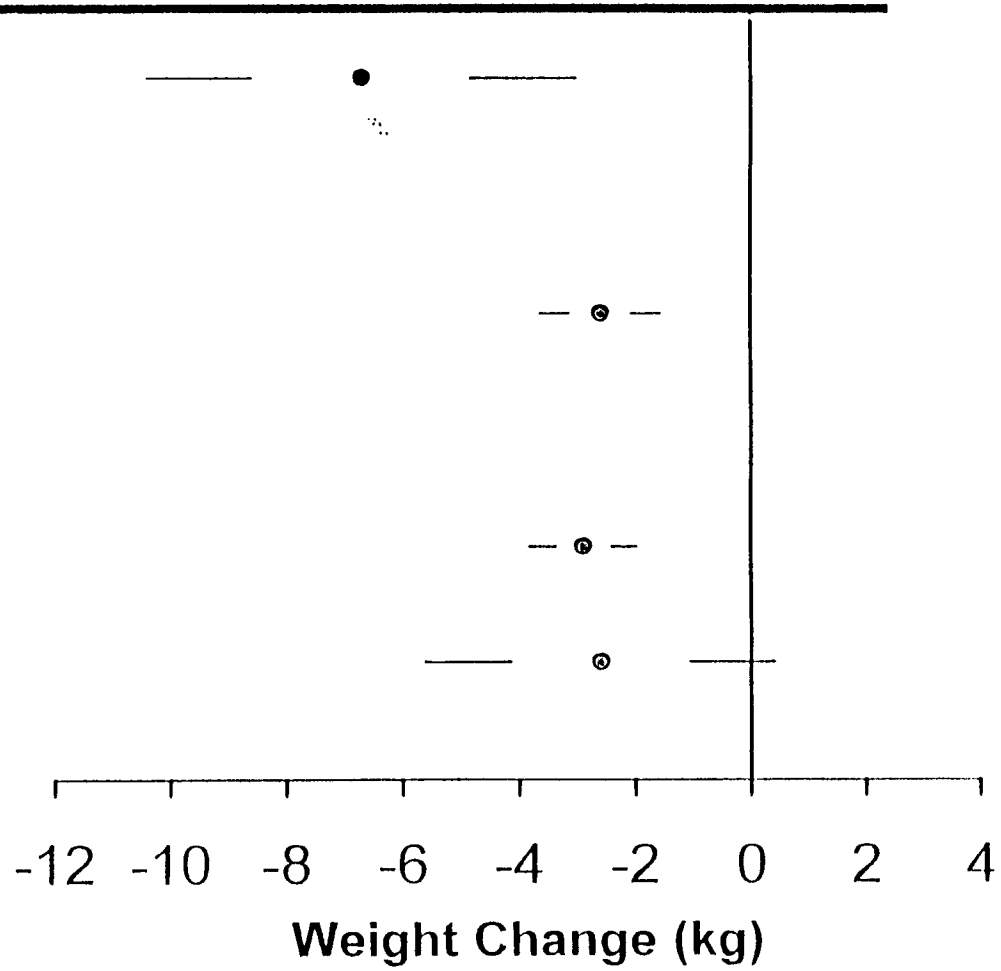
Treatment Effect Differences by Study
UK 18, P003, Noble and Index Studies

UK 18, PBO n=20/DF n=22

P003, PBO n=81/ 30 mg DFn=77

Noble, PBO n=27/DF n=28

Index, PBO n=467/DF n=463



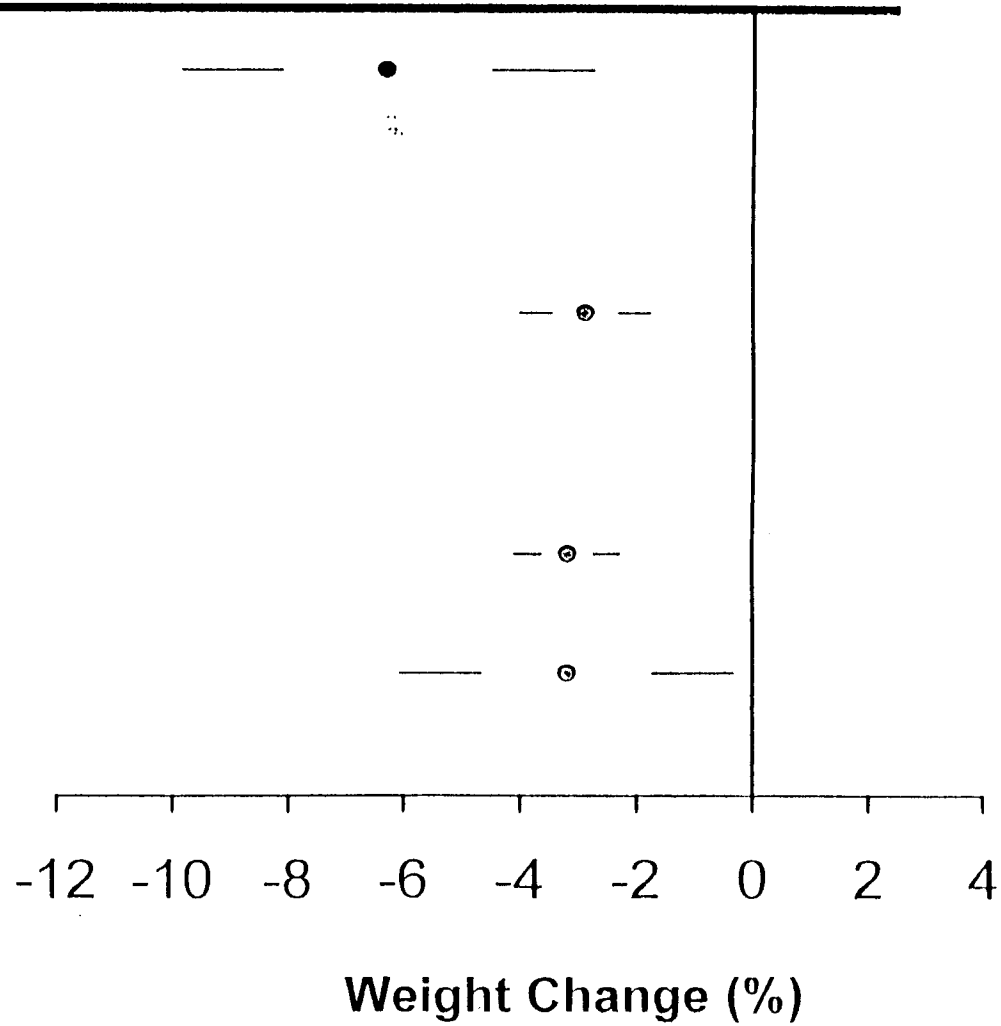
Treatment Effect Differences by Study
UK 18, P003, Noble and Index Studies

UK 18, PBO n=20/DF n=22

P003, PBO n=81/ 30 mg DFn=77

Noble, PBO n=27/DF n=28

Index, PBO n=467/DF n=463

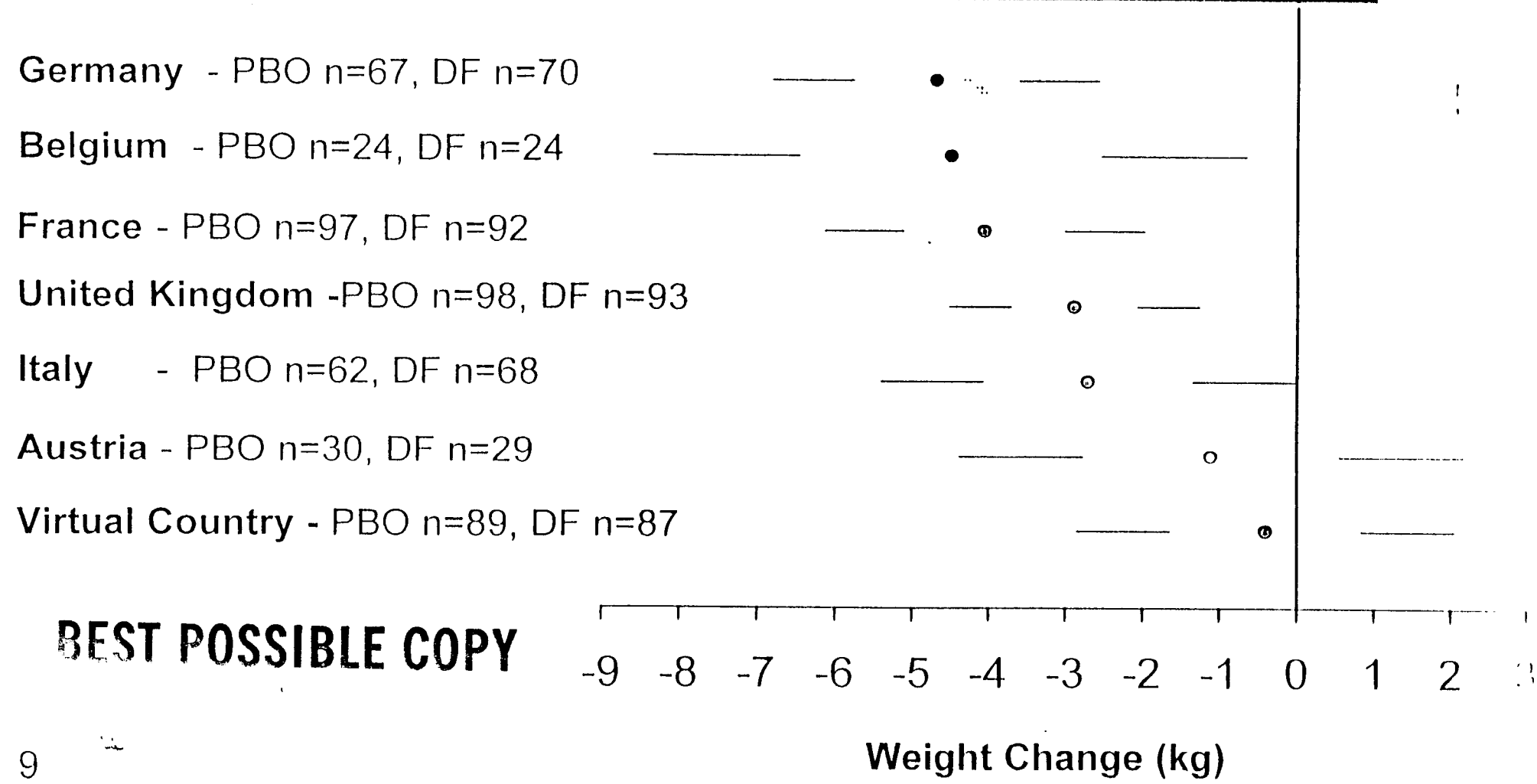


TWO TIERED ERROR BAR PLOTS

DIFFERENCES BY CENTER

INDEX STUDY

Treatment Effect Differences by Center
Index Study



Treatment Effect by Center Index Study

Belgium - DF n=24, PBO n=24

Germany - DF n=70, PBO n=67

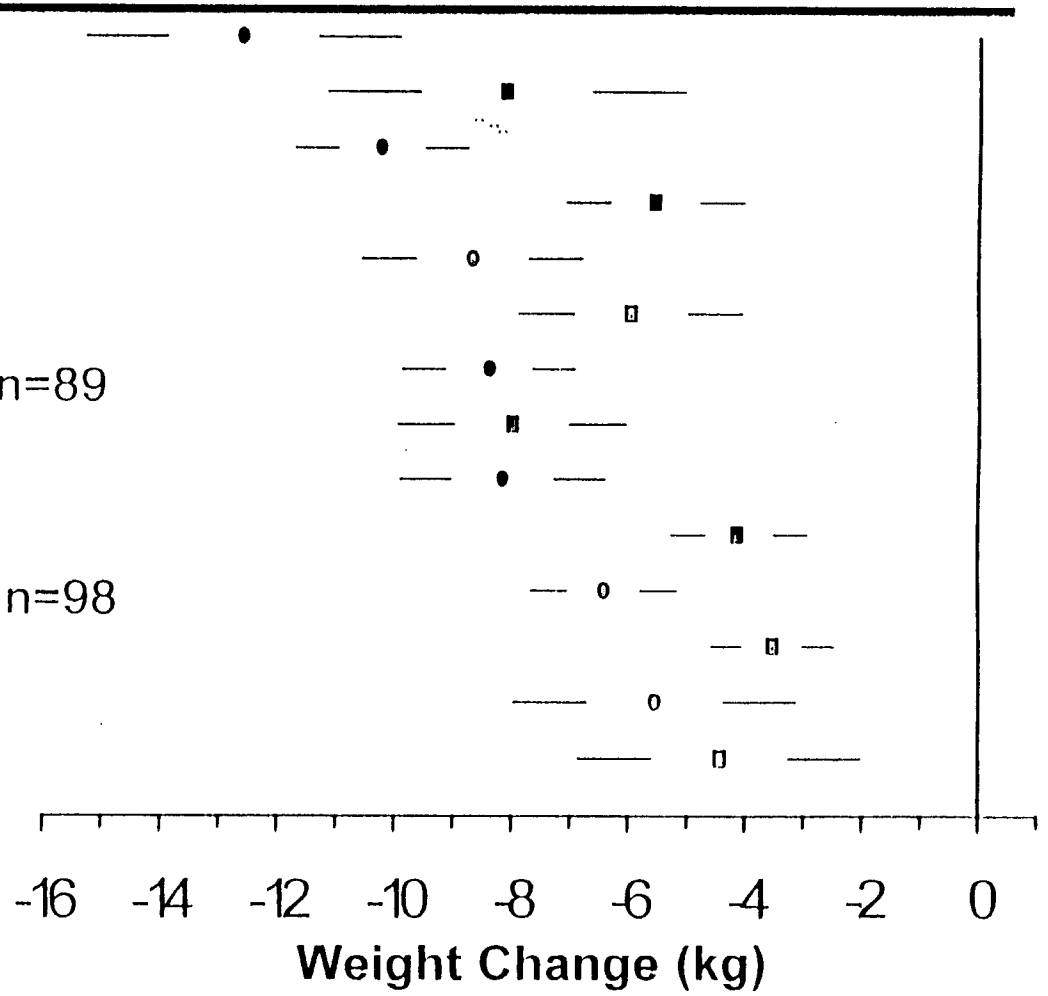
Italy - DF n=68, PBO n=62

Virtual Country - DF n=87, PBO n=89

France - DF n=92, PBO n=97

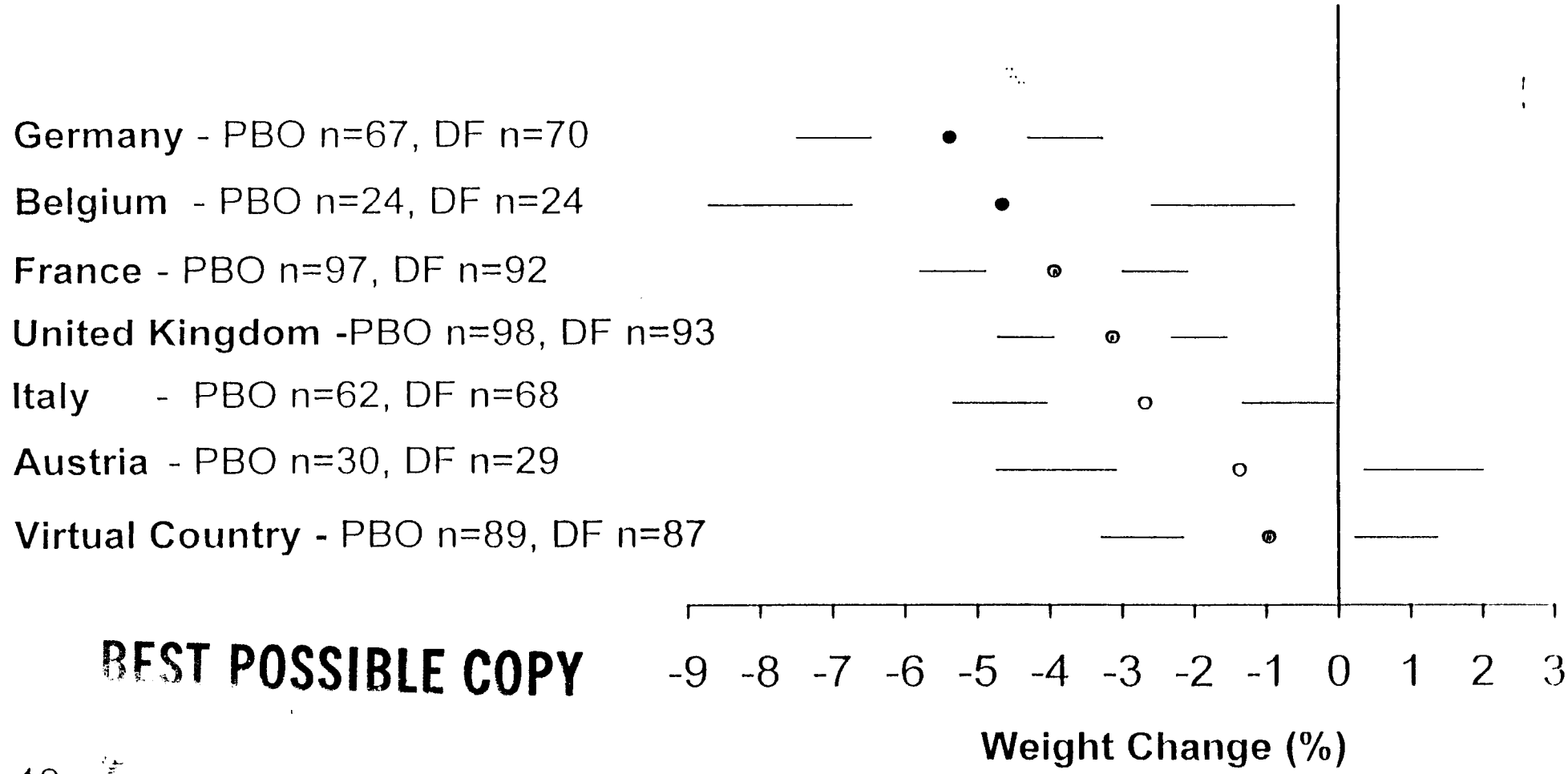
United Kingdom -DF n=93, PBO n=98

Austria - DF n=29, PBO n=30



Circle --> Active
Square --> Placebo

Treatment Effect Differences by Center
Index Study



Treatment Effect by Center
Index Study

Belgium - DF n=24, PBO n=24

Germany - DF n=70, PBO n=67

Italy - DF n=68, PBO n=62

Virtual Country - DF n=87, PBO n=89

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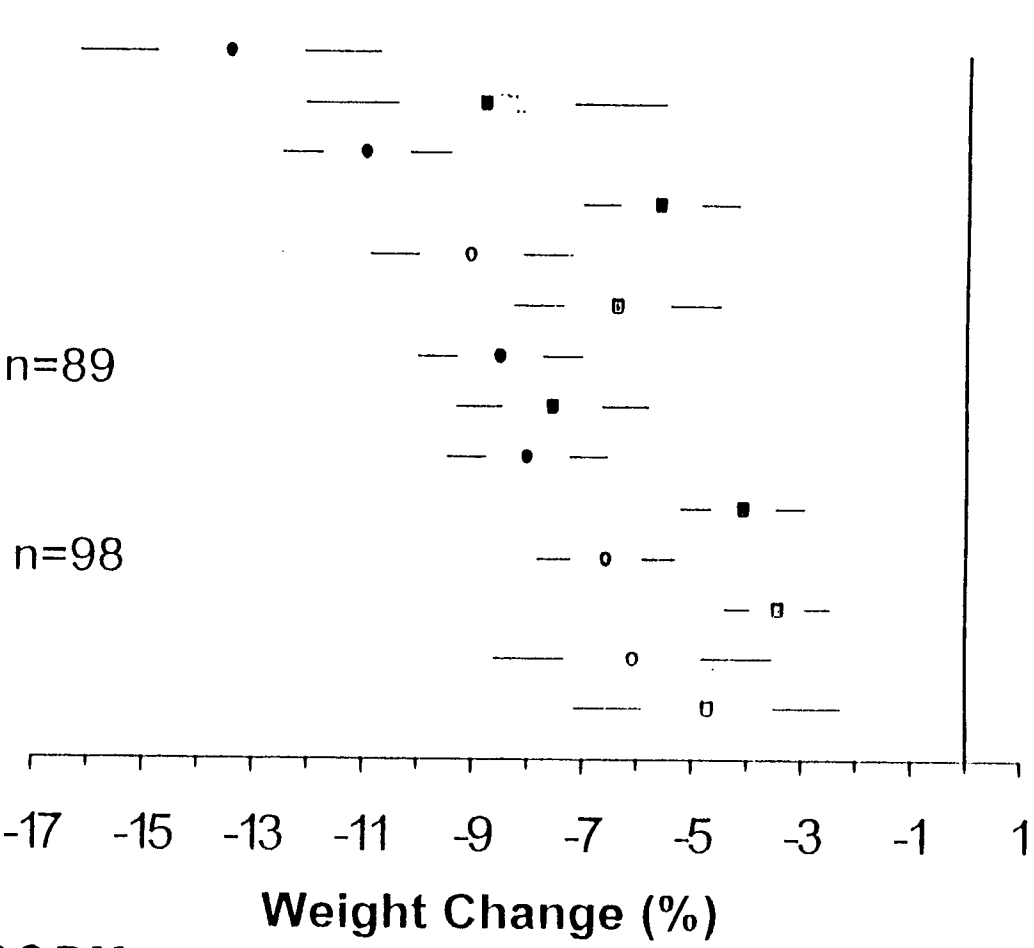
Austria - DF n=29, PBO n=30

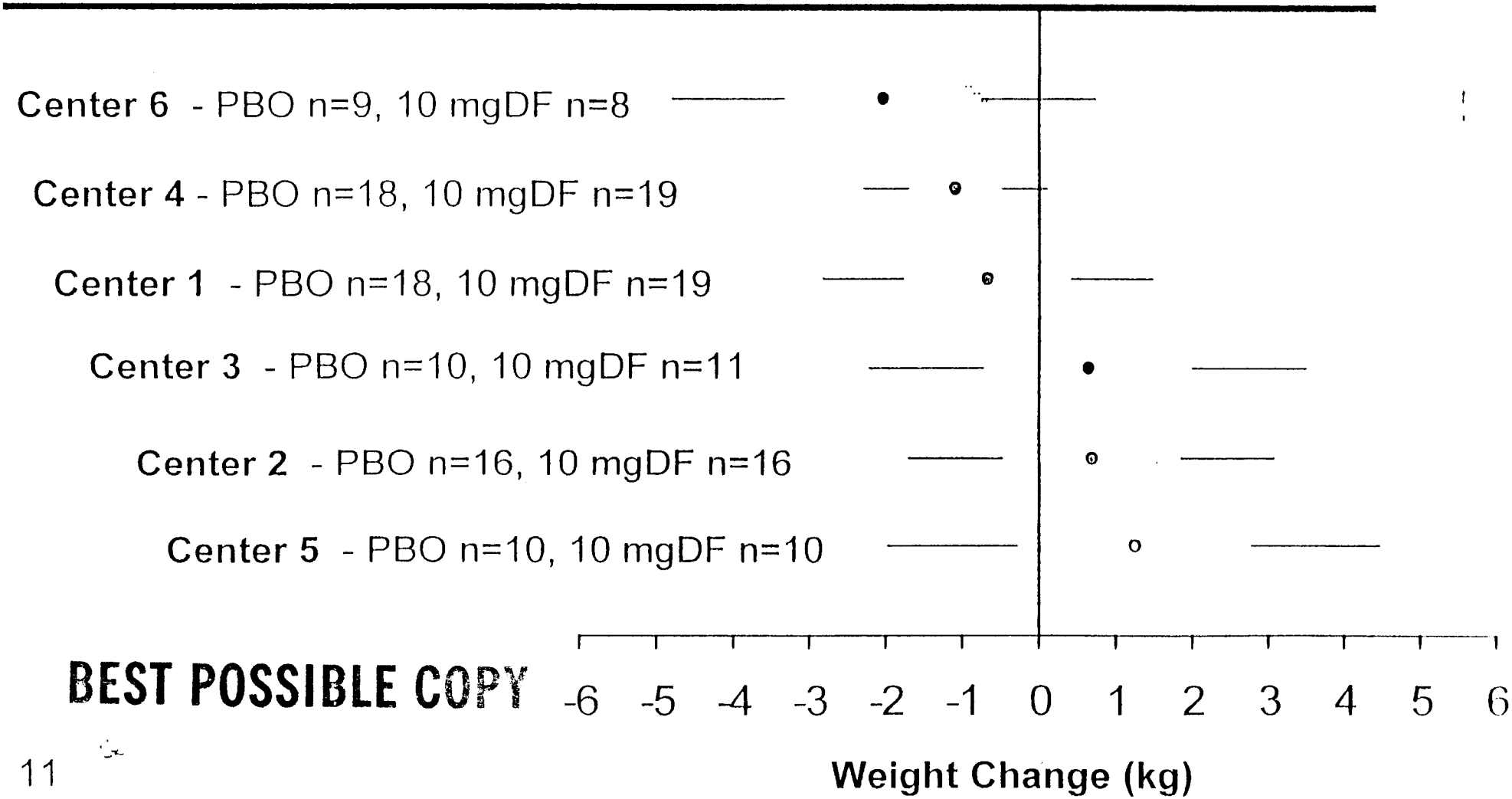


Circle --> Active
Square --> Placebo

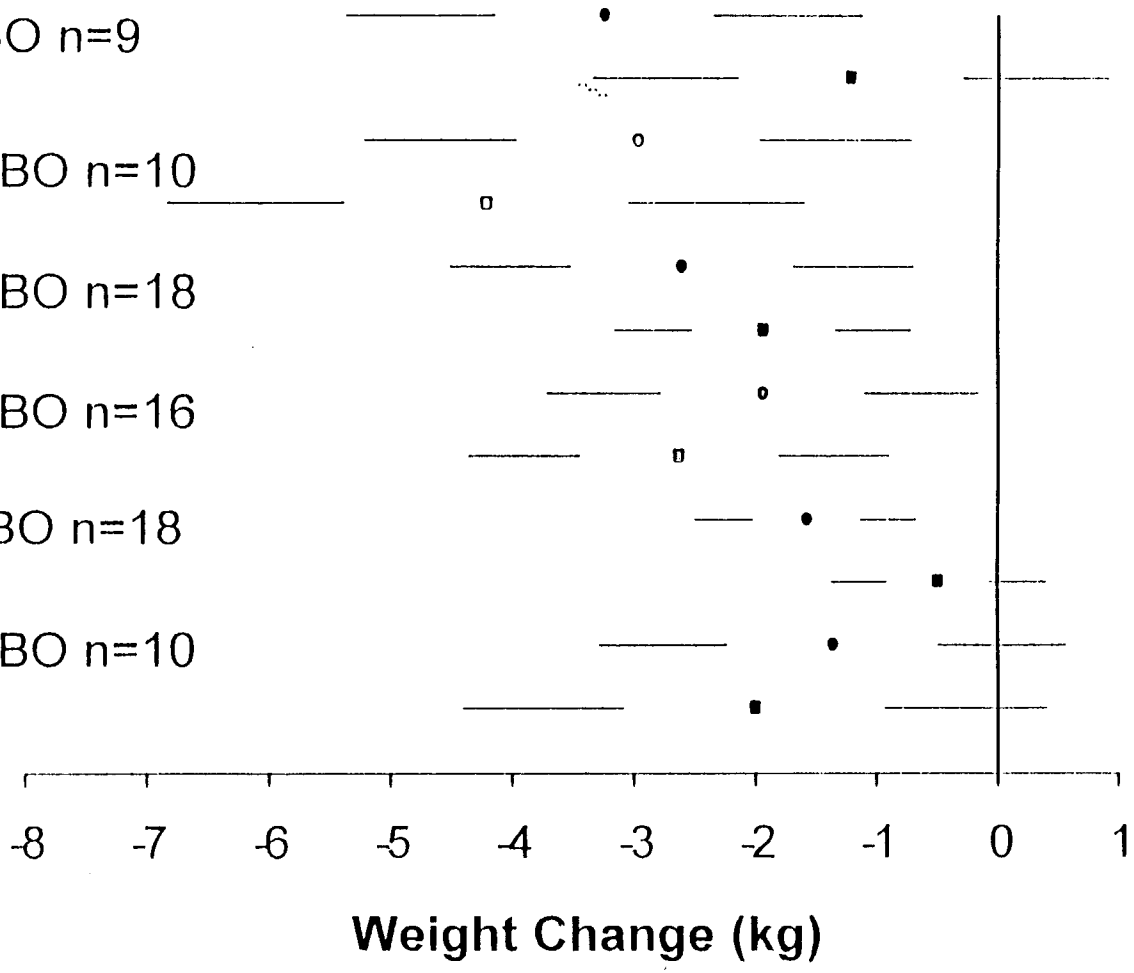
TWO TIERED ERROR BAR PLOTS OF TREATMENT EFFECT DIFFERENCES BY CENTER AND DOSE

STUDY IP92-003

Treatment Effect Differences by Center and Dose
P003 Study

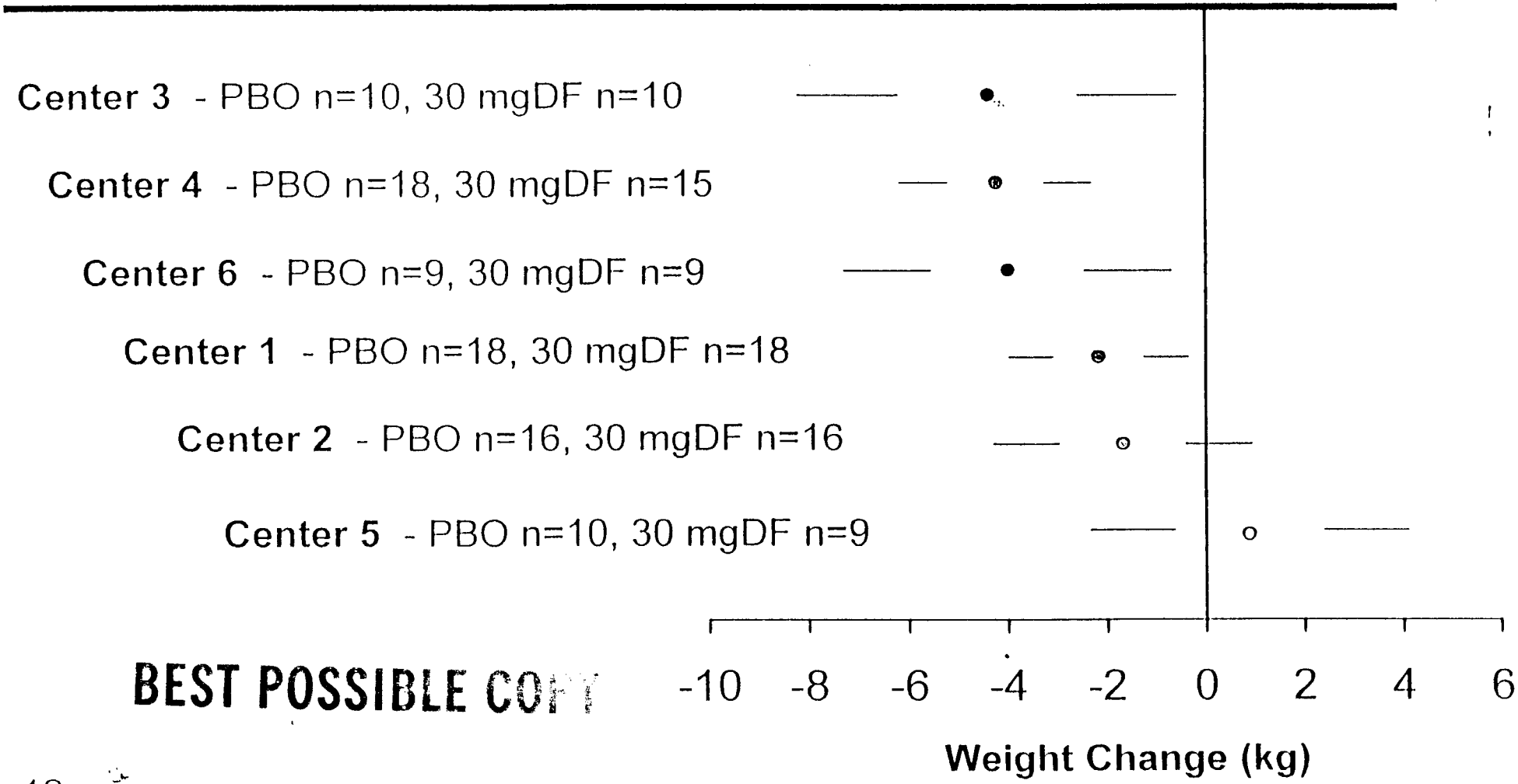


Treatment Effect by Center and Dose
P003 Study



Circle --> Active
Square --> Placebo

Treatment Effect Differences by Center and Dose
P003 Study



Treatment Effect by Center and Dose
P003 Study

Center 3 - 30 mgDF n=10, PBO n=10

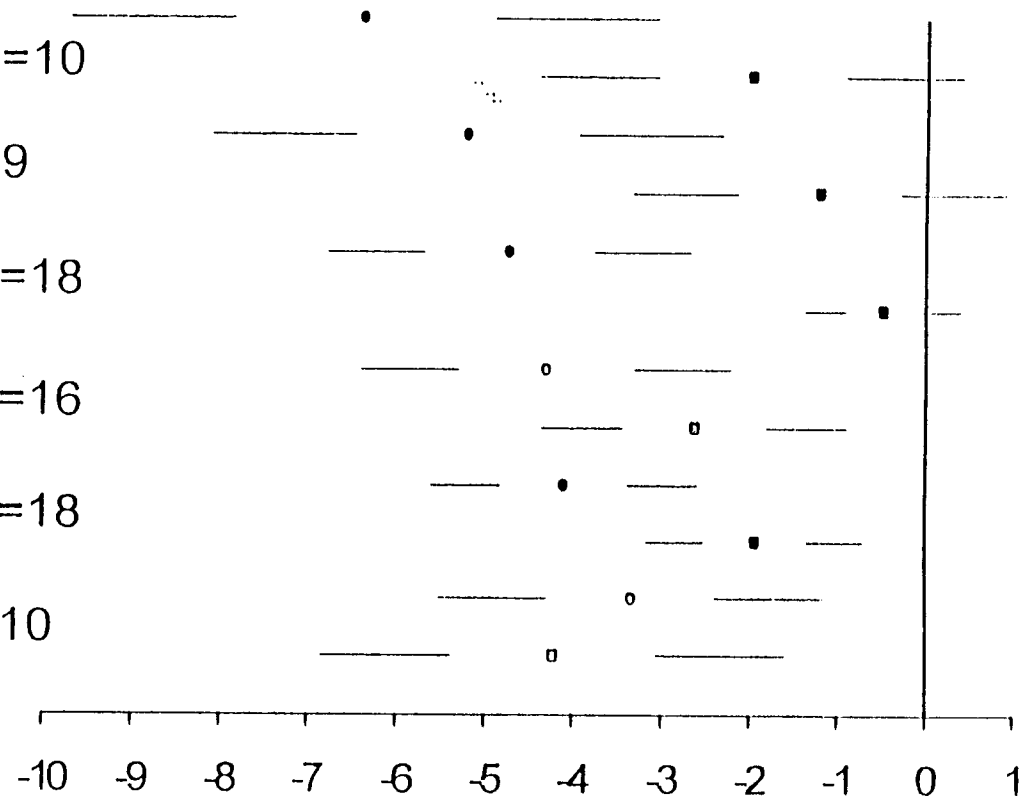
Center 6 - 30 mgDF n=9, PBO n=9

Center 4 - 30 mgDF n=15, PBO n=18

Center 2 - 30 mgDF n=16, PBO n=16

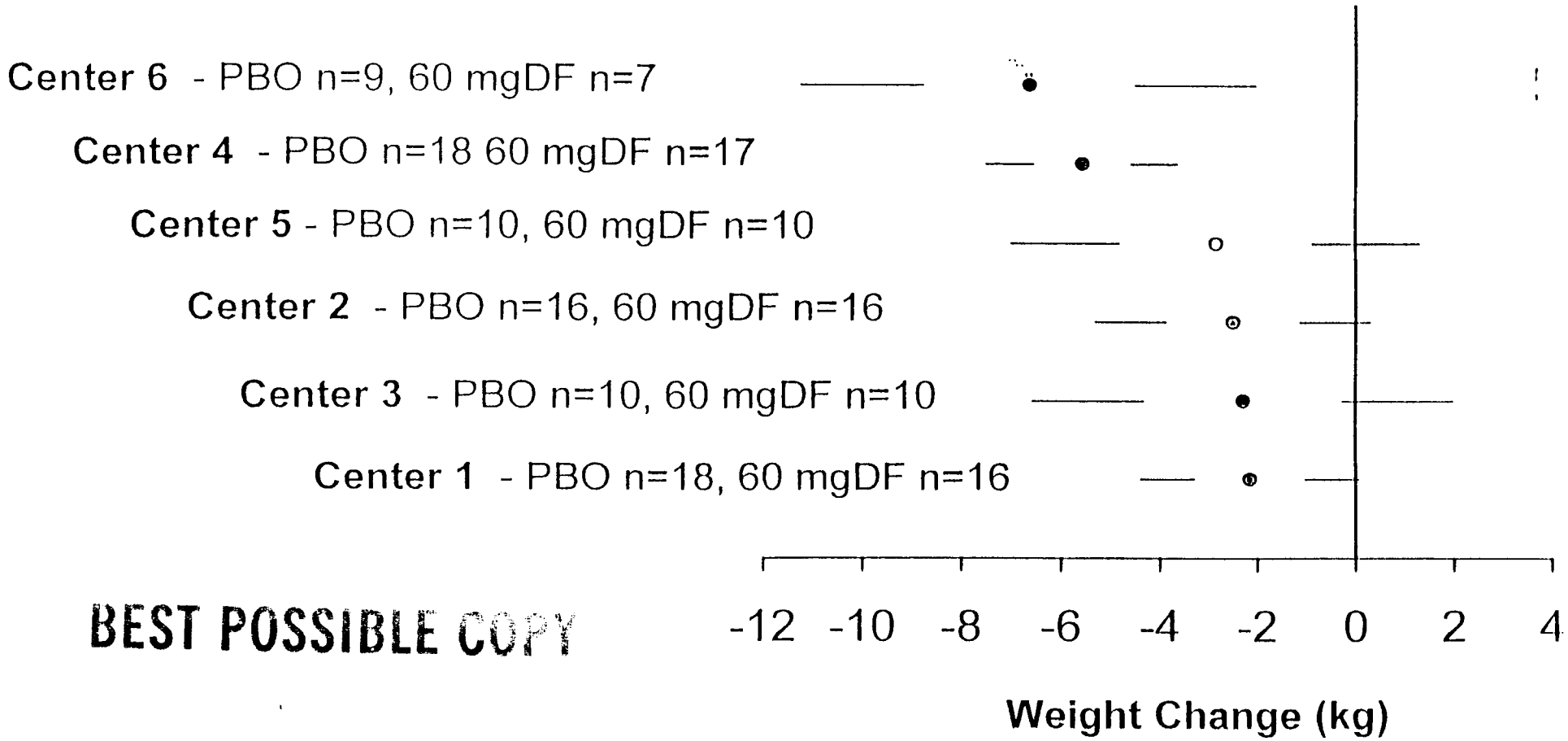
Center 1 - 30 mgDF n=18, PBO n=18

Center 5 - 30 mgDF n=9, PBO n=10

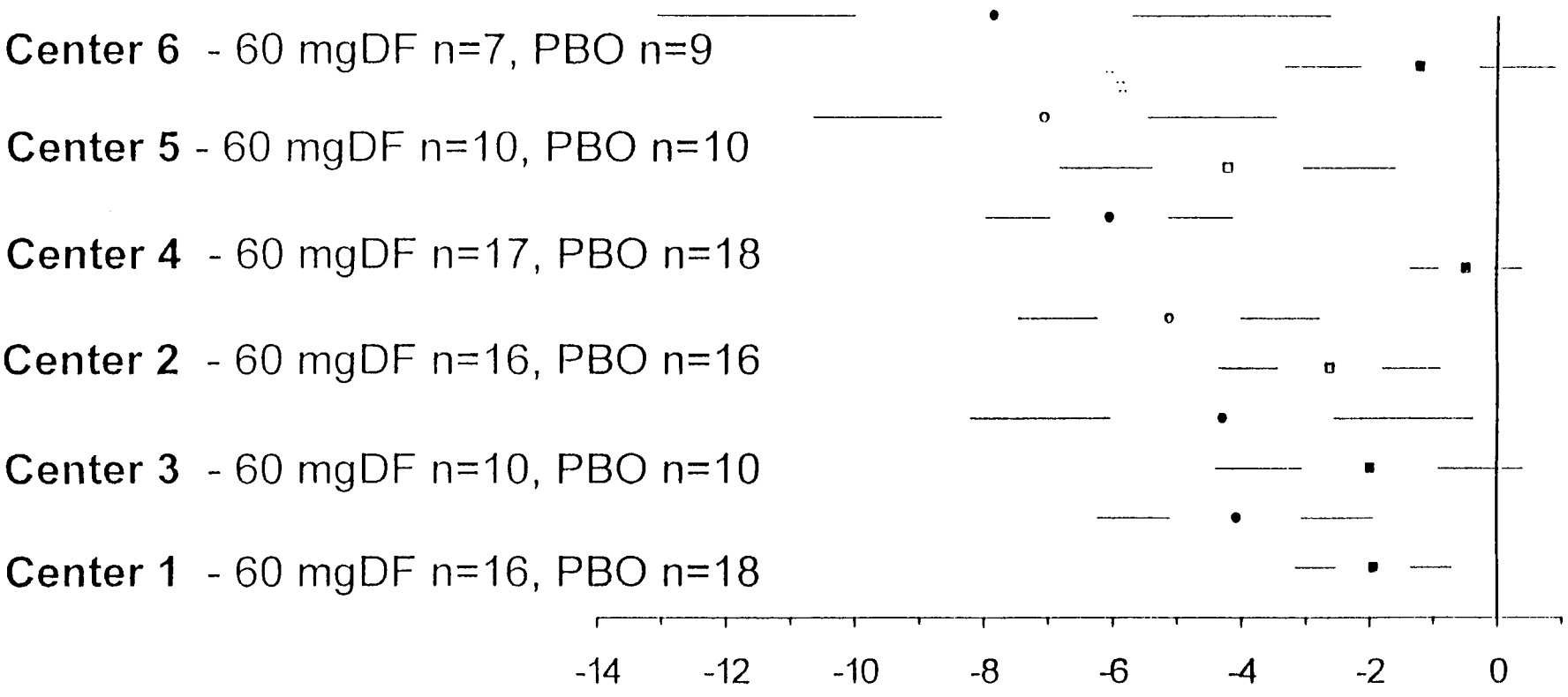


Circle --> Active
Square --> Placebo

Treatment Effect Differences by Center and Dose P003 Study

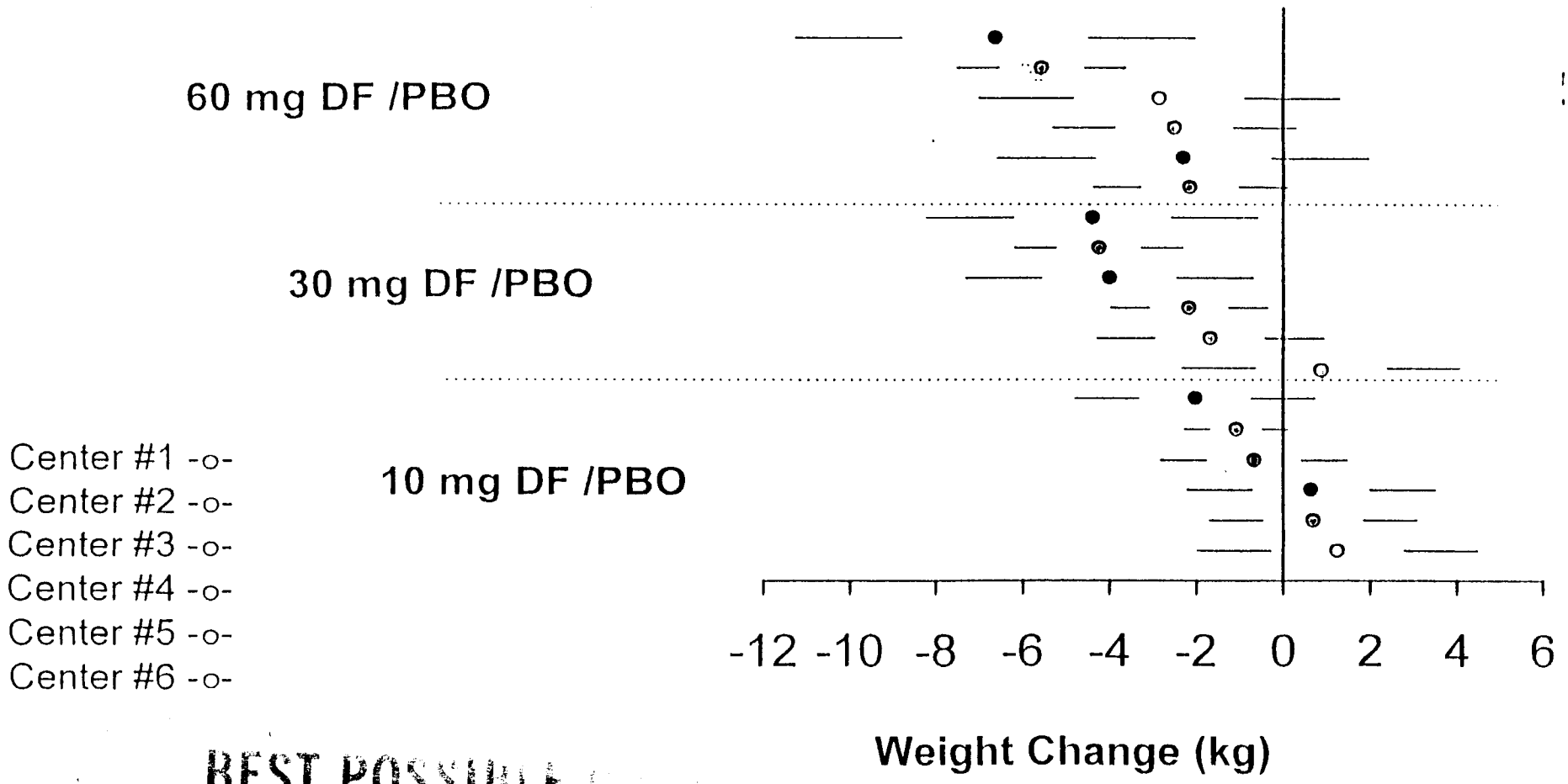


Treatment Effect by Center and Dose
P003 Study

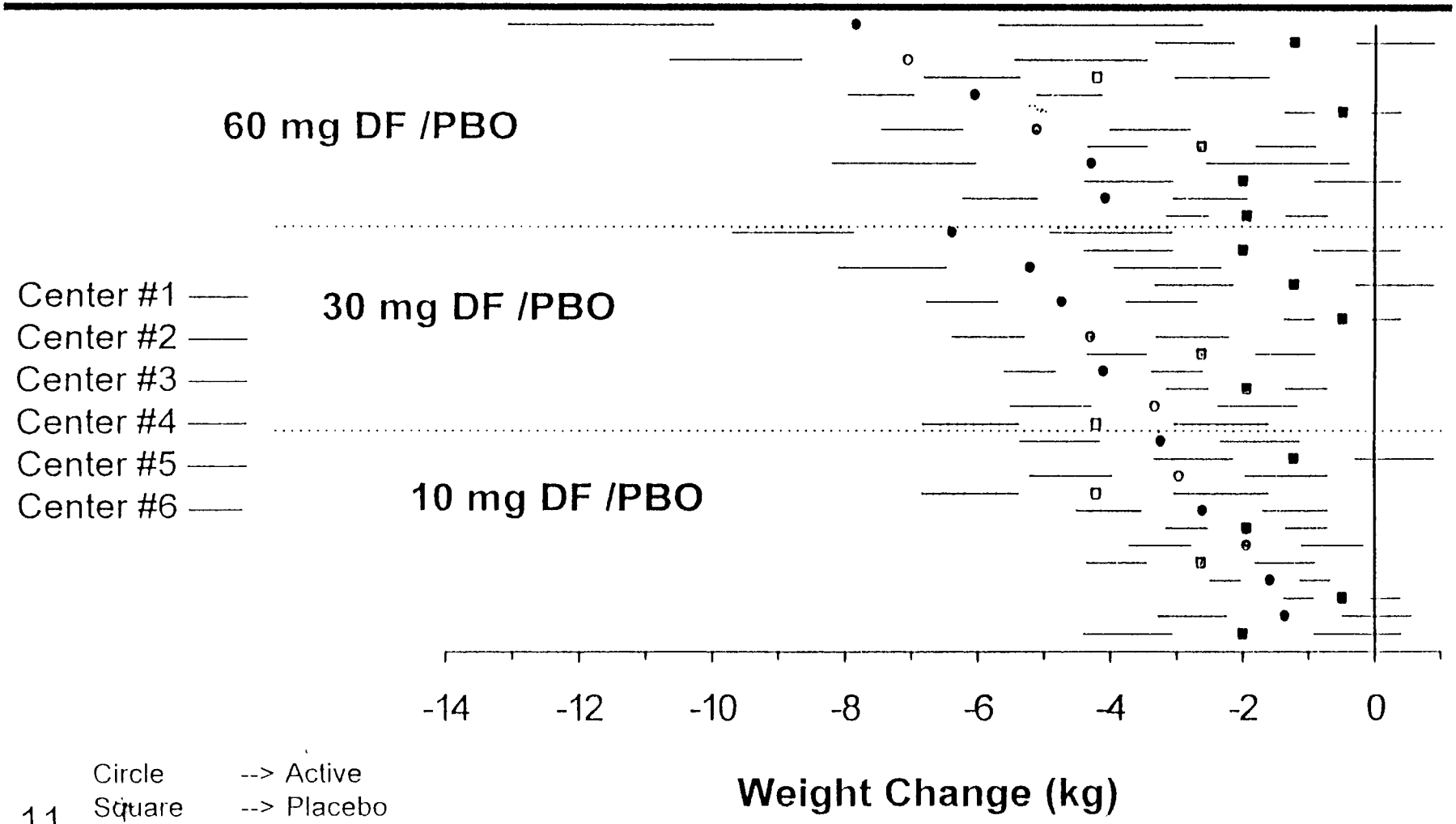


Circle --> Active
Square --> Placebo

Treatment Effect Differences by Center and Dose
P003 Study



Treatment Effect by Center and Dose
P003 Study



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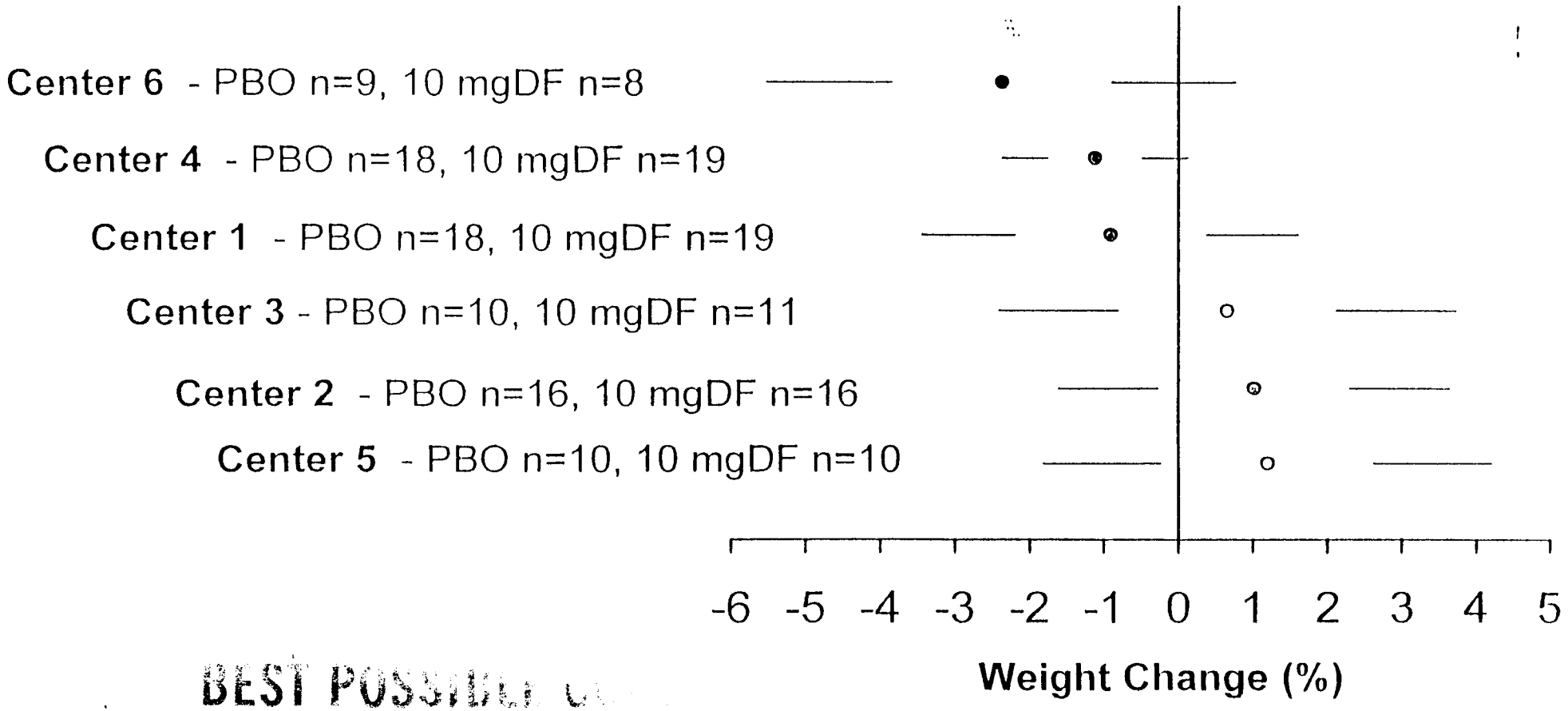
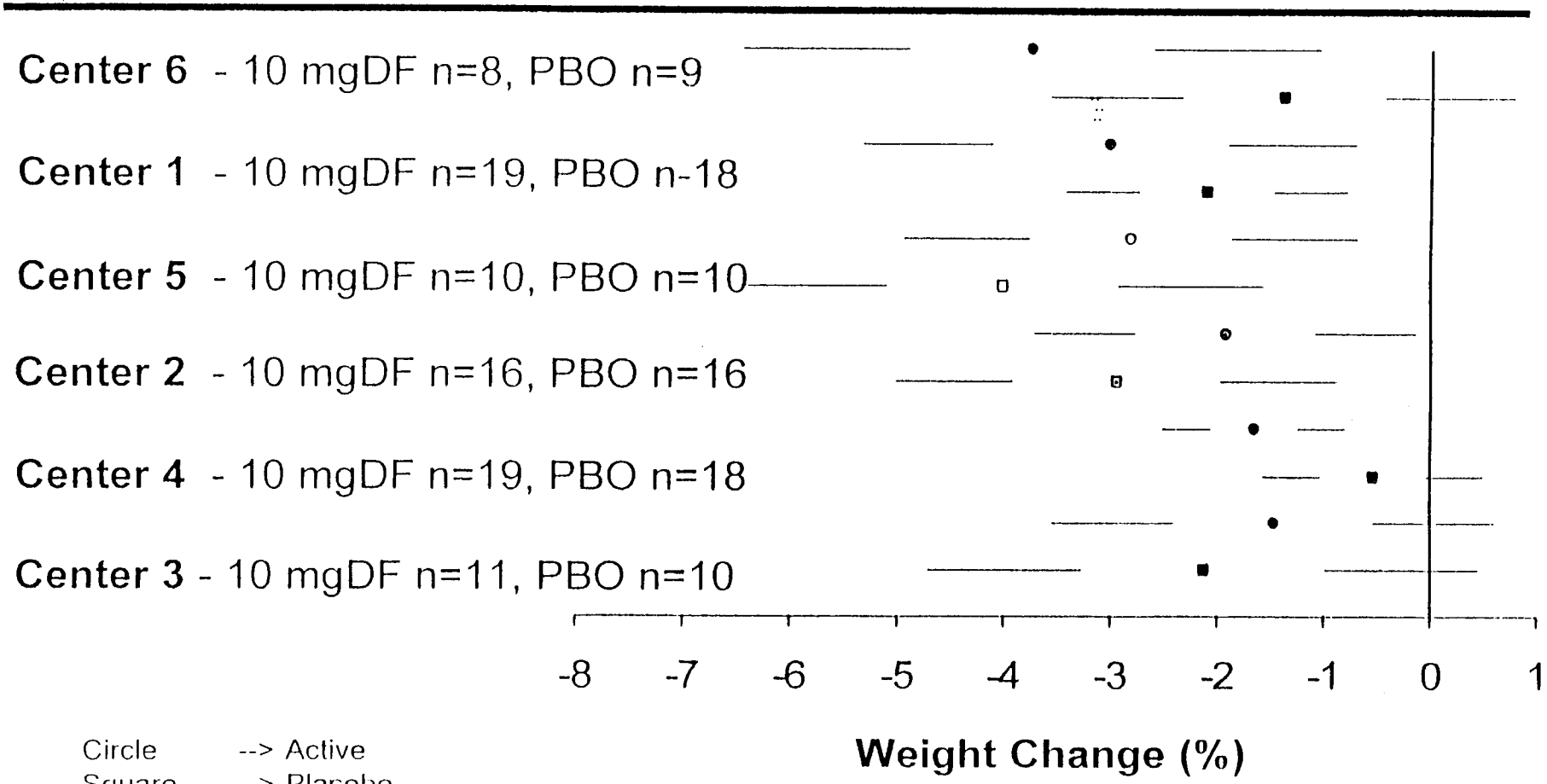
Treatment Effect Differences by Center and Dose
P003 Study



Treatment Effect by Center and Dose
P003 Study



Circle --> Active
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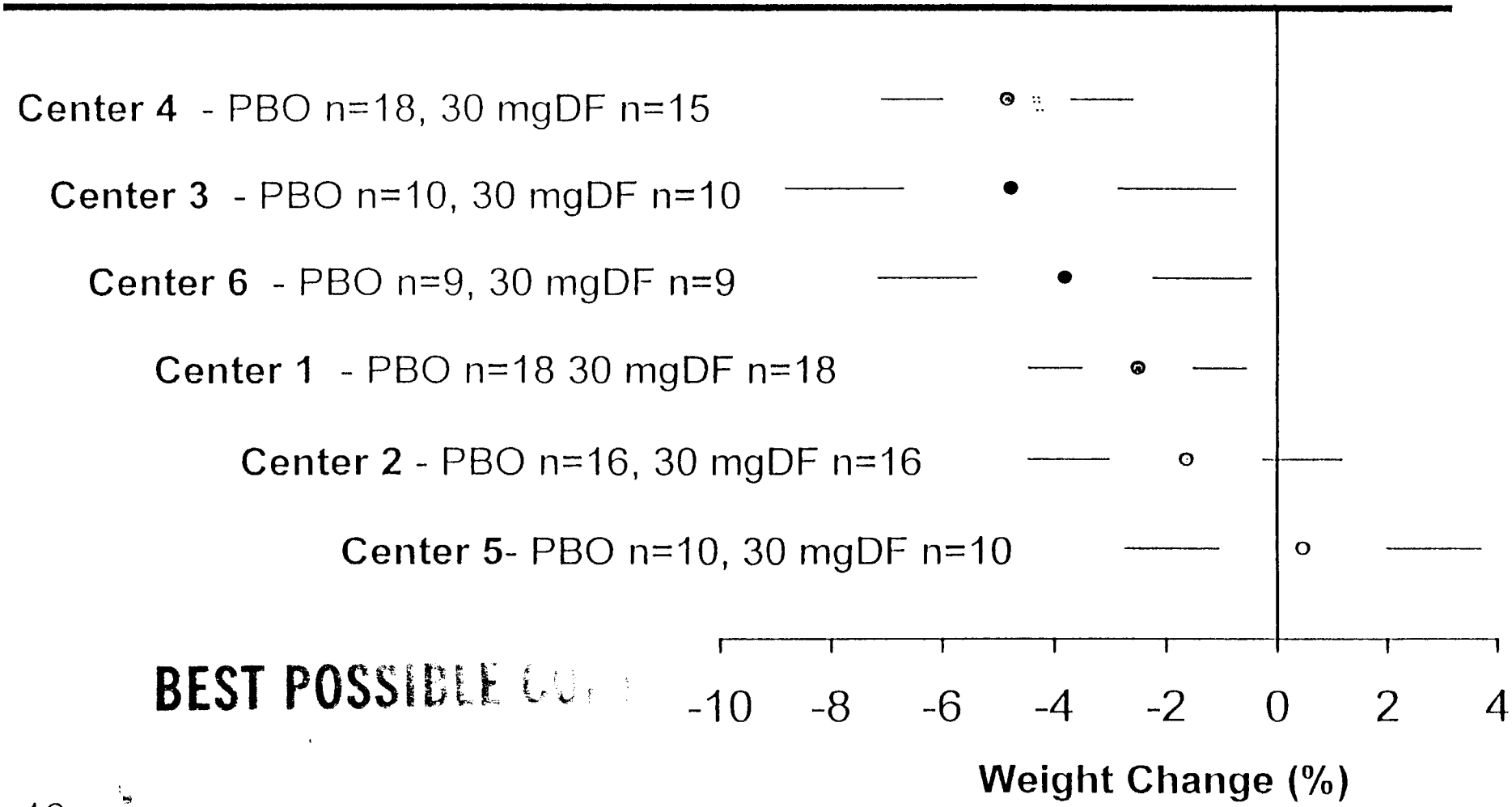
Treatment Effect Differences by Center and Dose P003 Study



Treatment Effect by Center
P003 Study

Center 3 - 30 mgDF n=10, PBO n=10

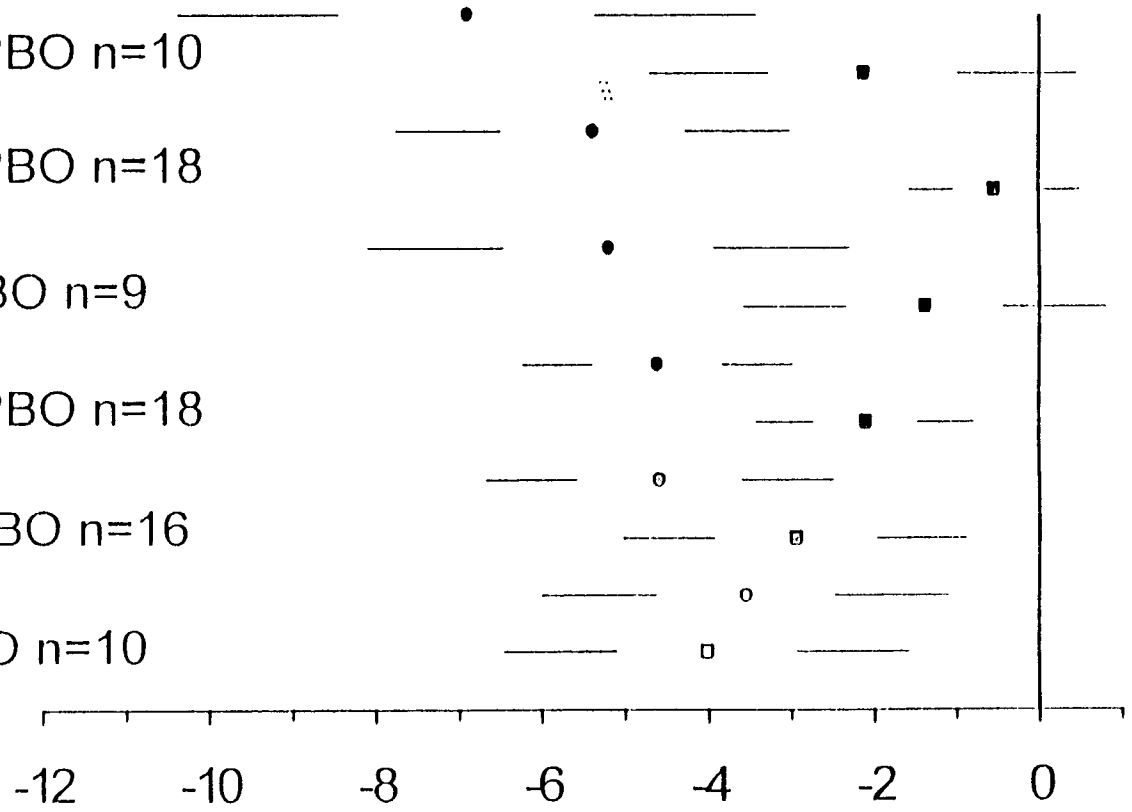
Center 4 - 30 mgDF n=15, PBO n=18

Center 6 - 30 mgDF n=9, PBO n=9

Center 1 - 30 mgDF n=18, PBO n=18

Center 2 - 30 mgDF n=16, PBO n=16

Center 5- 30 mgDF n=9, PBO n=10



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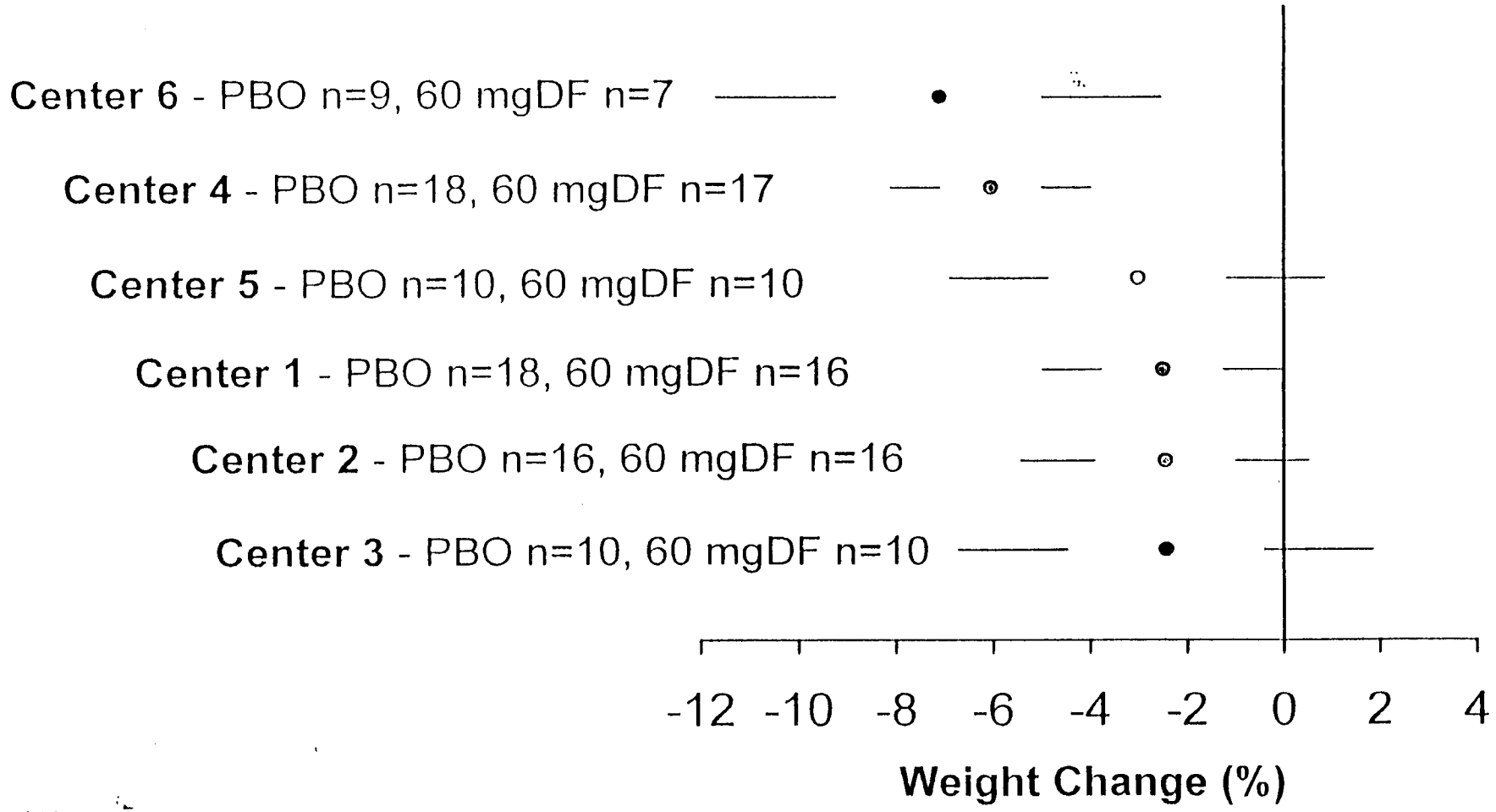
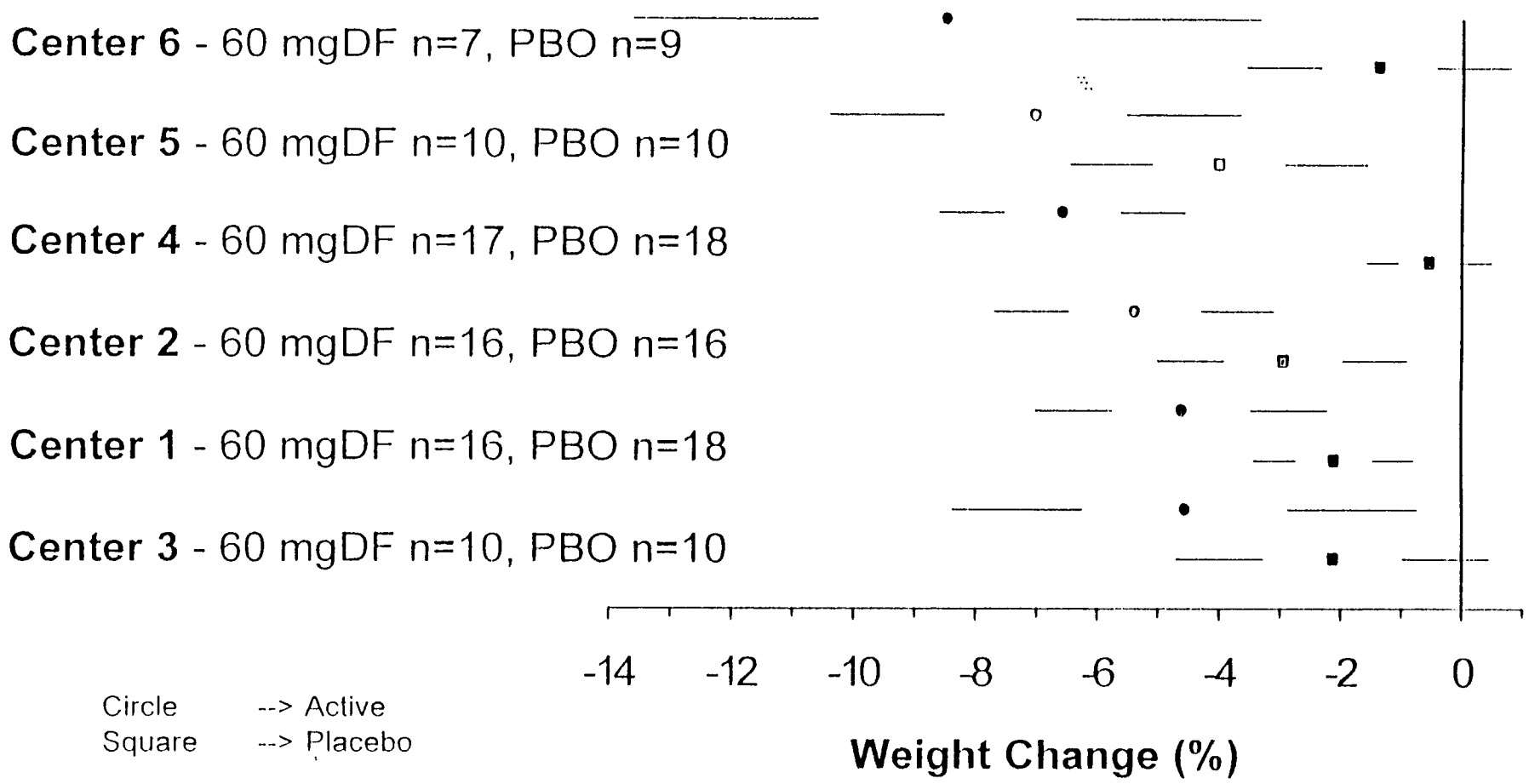
Treatment Effect Differences by Center and Dose
P003 Study



Treatment Effect by Center
P003 Study



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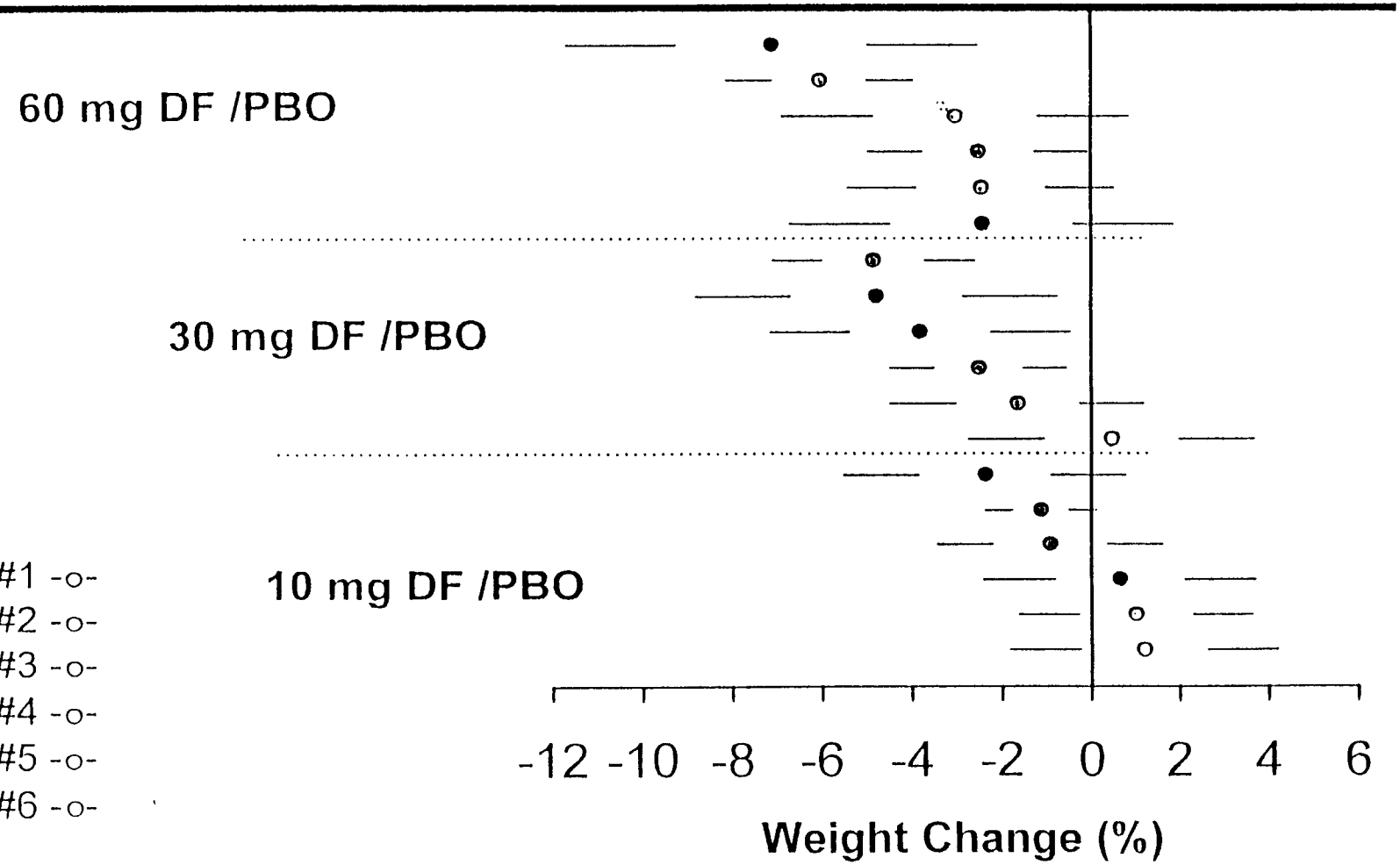
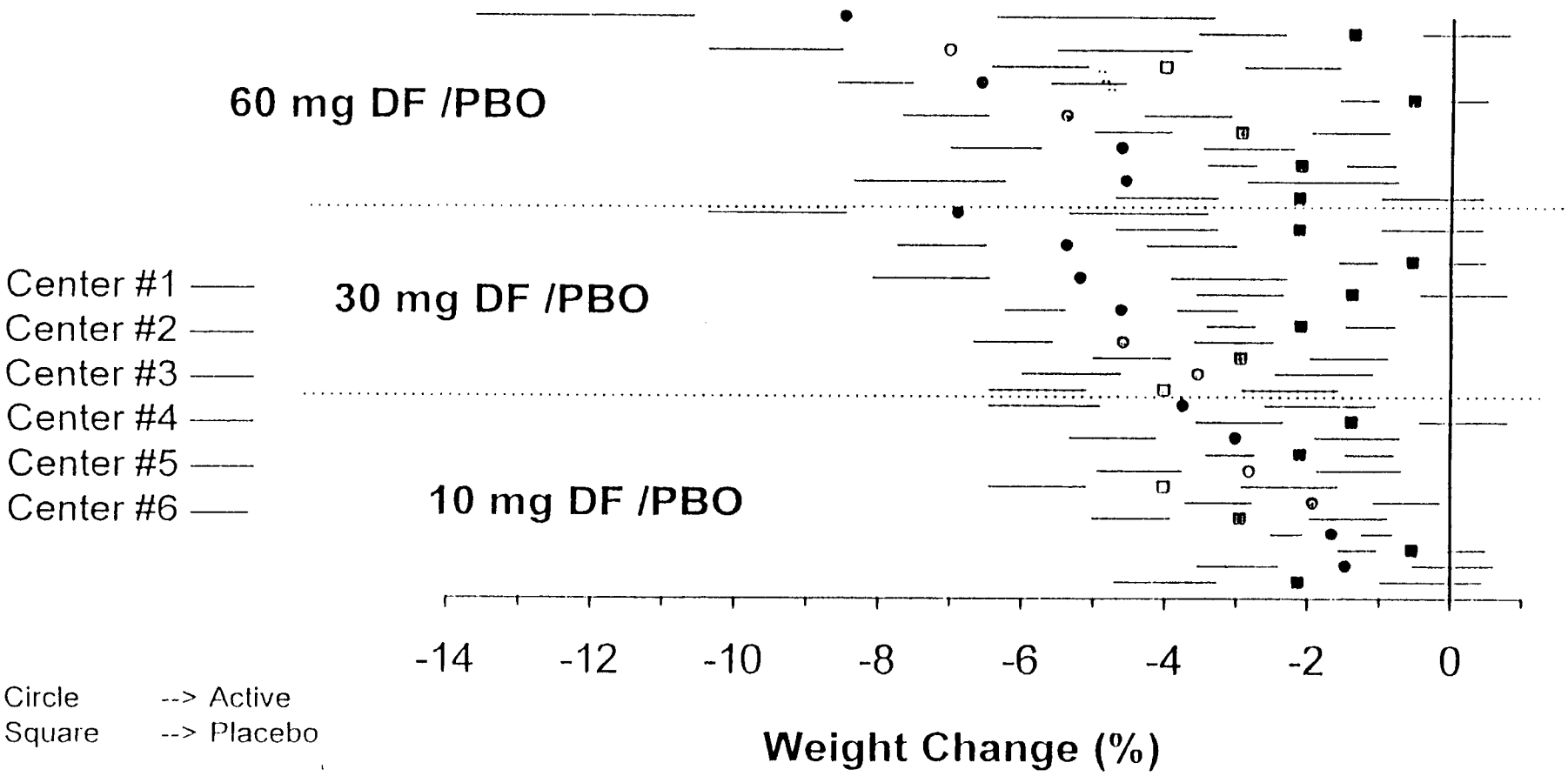
Treatment Effect Differences by Center and Dose
P003 Study



Treatment Effect by Center and Dose
P003 Study



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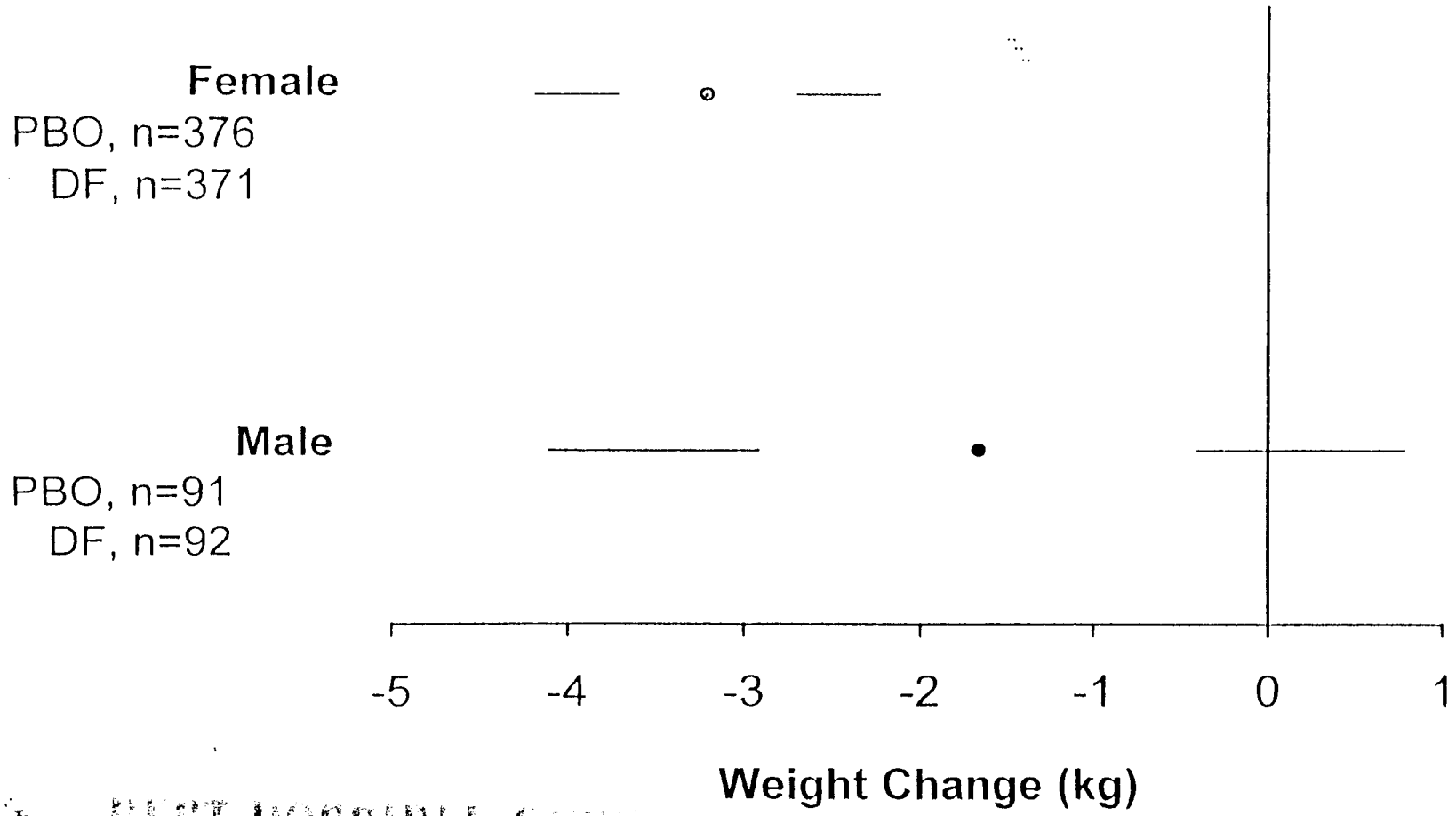
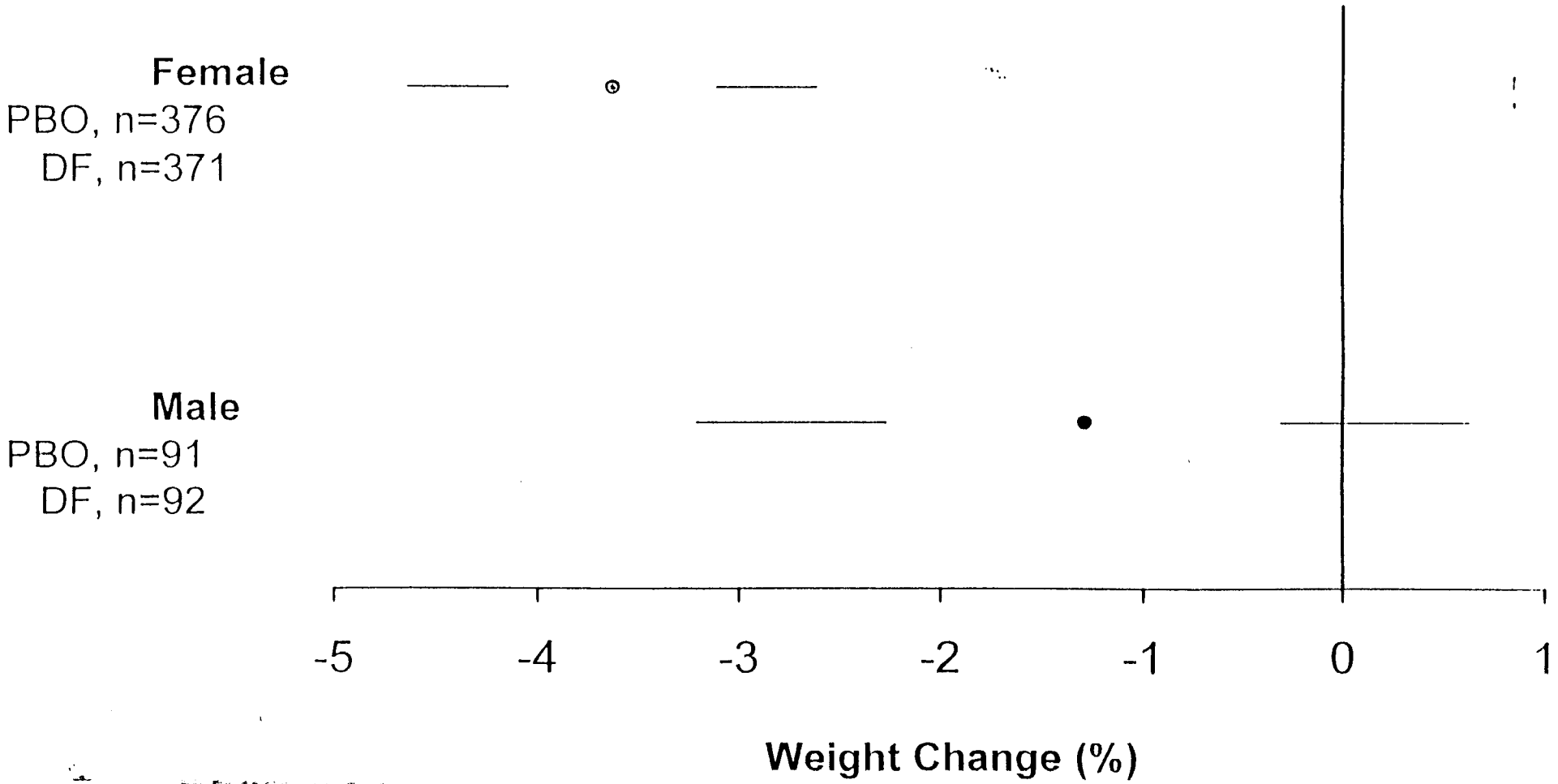
TREATMENT EFFECT DIFFERENCES BY GENDER

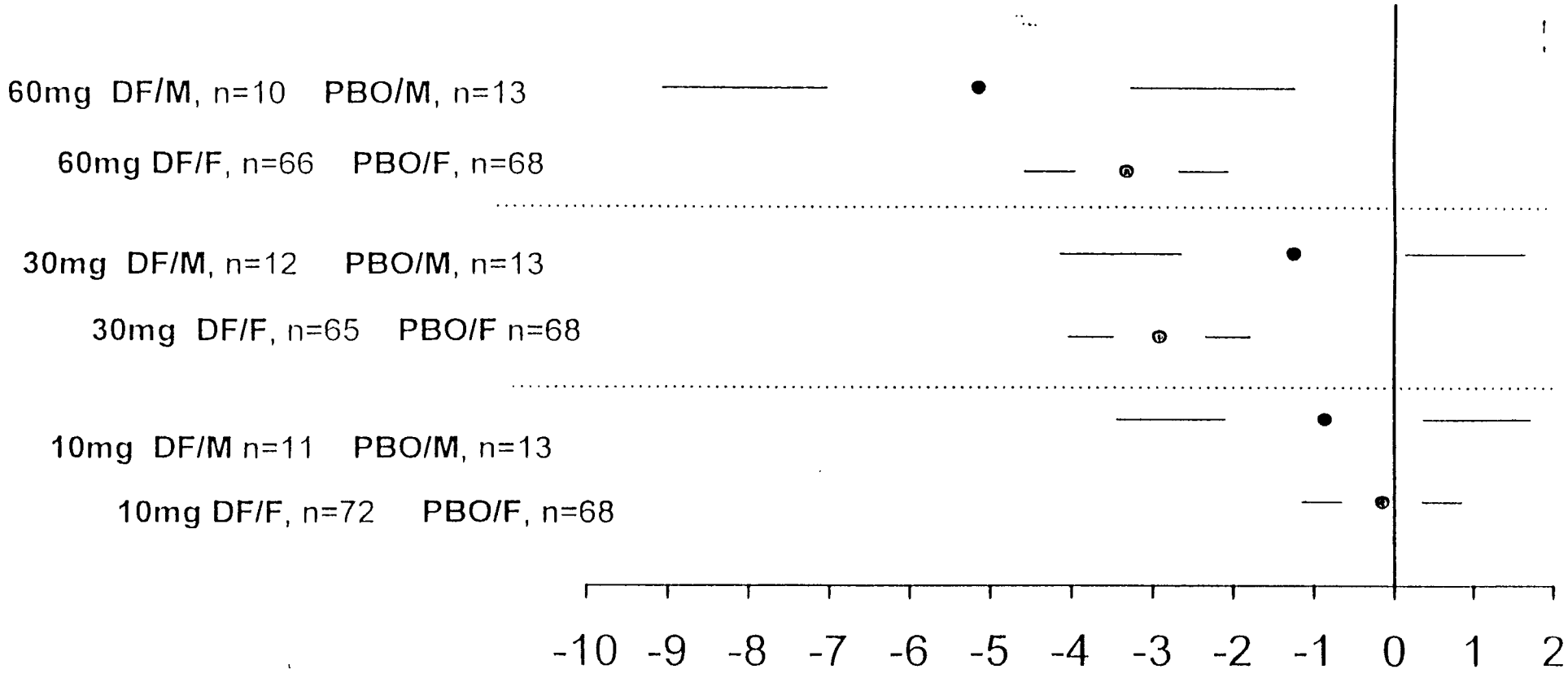
Treatment Effect Differences by Gender
Index Study



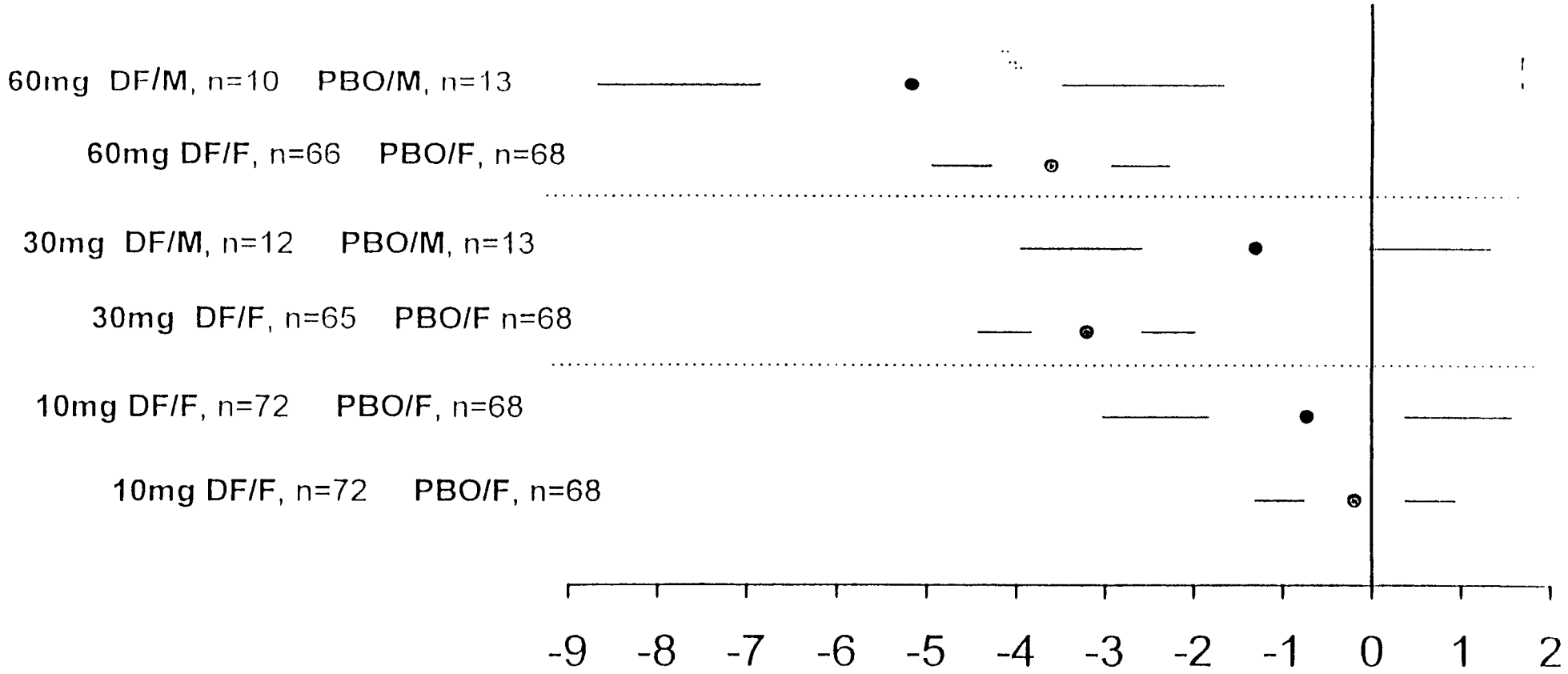
Treatment Effect Differences by Gender Index Study



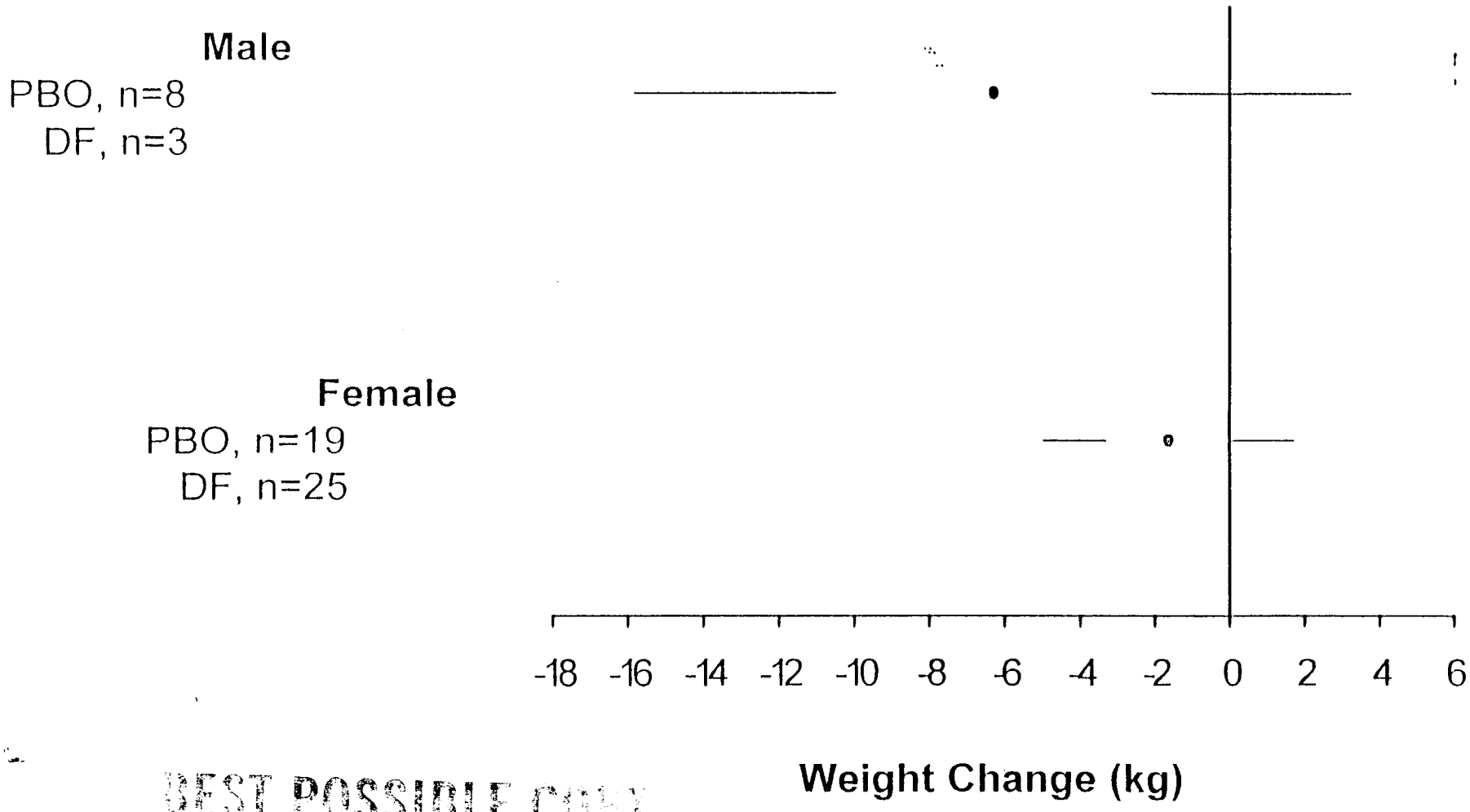
Treatment Effect Differences by Gender and Dose
P003 Study



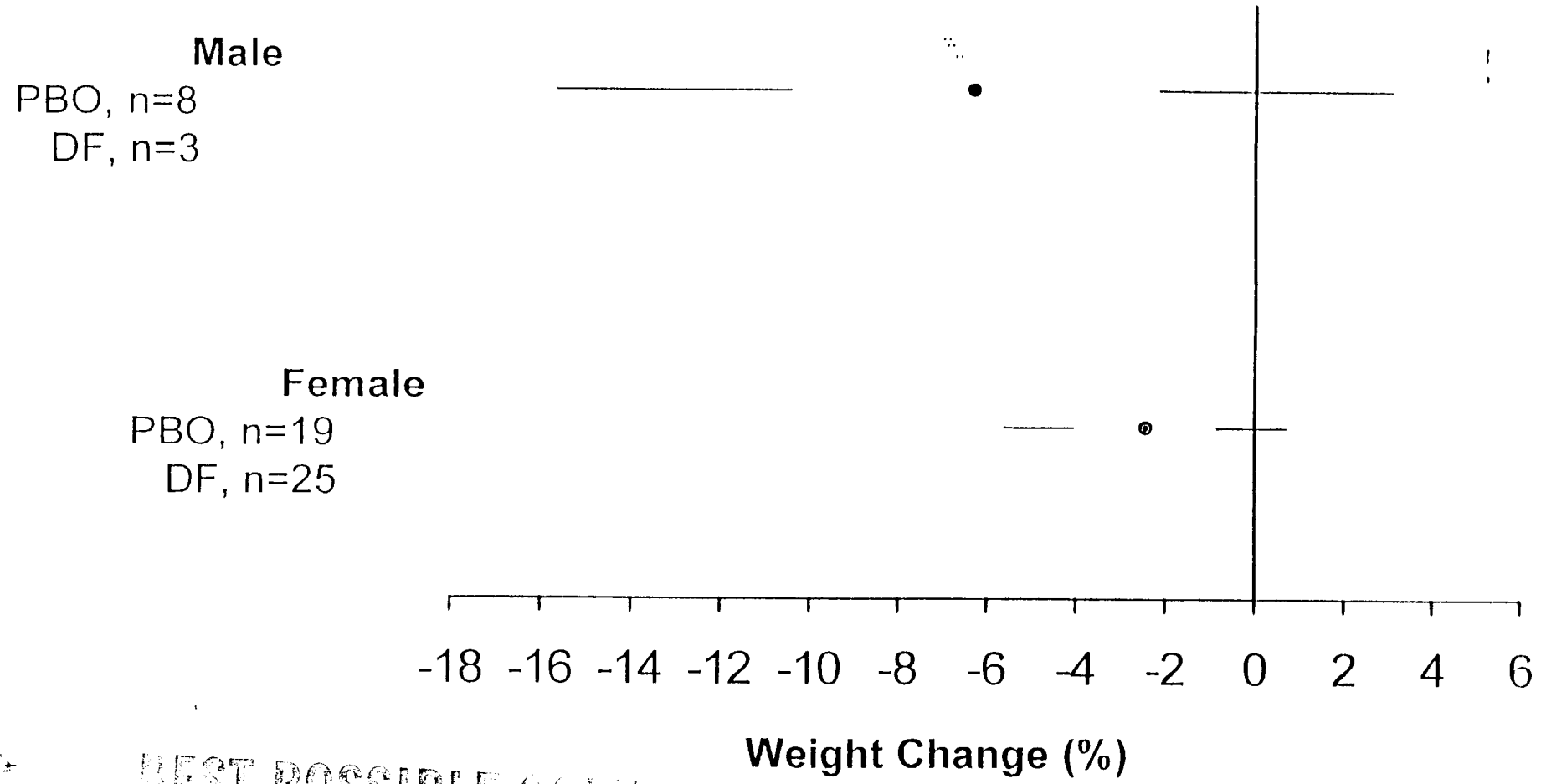
Treatment Effect Differences by Gender and Dose P003



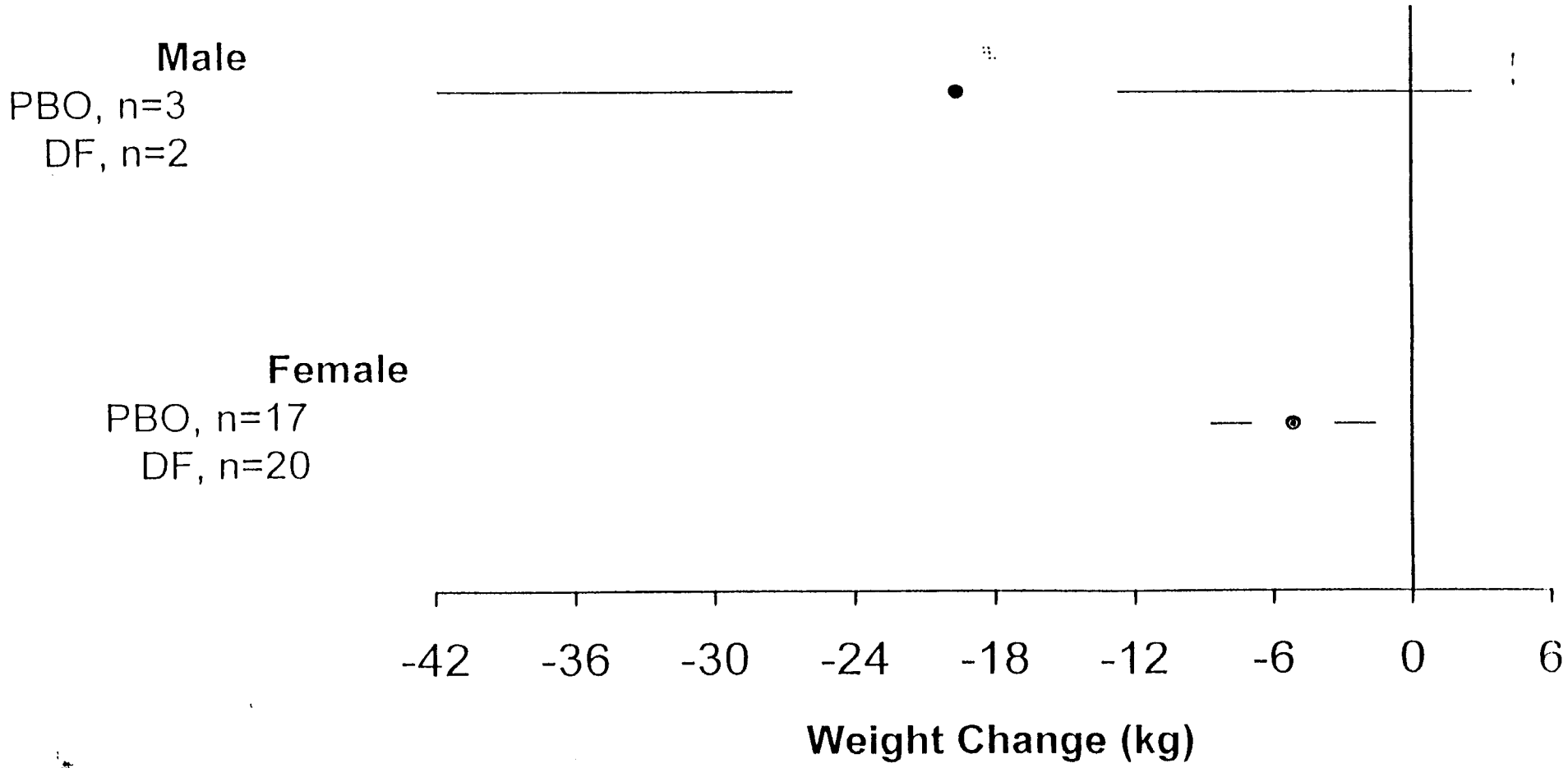
Treatment Effect Differences by Gender
Noble Study



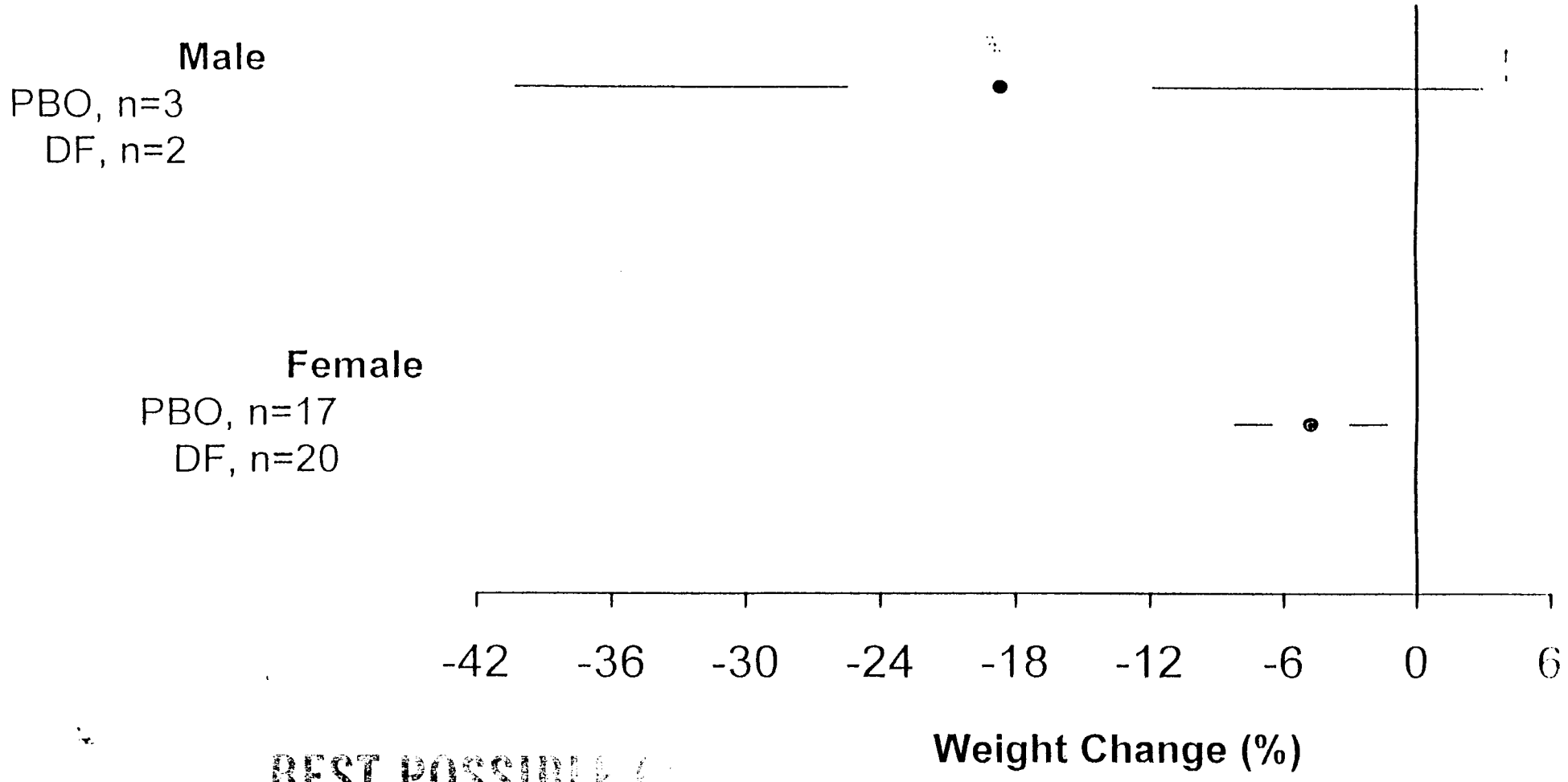
Treatment Effect Differences by Gender
Noble Study



Treatment Effect Differences by Gender
UK18 Study



Treatment Effect Differences by Gender
UK18 Study



EXCEL SPREAD SHEETS

AND

DISKETTE CONTAINING SAME

	ppo n	dif n	ppo mean	dif mean	ppo sd	dif sd	SEM of dif	
male	91	92	-6.58	-8.24	6.47	8.45	1.250773771	
female	376	371	-5.13	-8.34	6.74	6.99	0.50238757	
male %	91	92	-5.7	-6.99	7.11	6.13	0.98102179	
female %	376	371	-5.36	-8.99	6.76	7.34	0.51619754	
male 10mg	13	11	-2.47	-3.34	3.19	2.82	1.240256725	
female 10mg	68	72	-1.86	-2.01	2.94	3.07	0.508582438	
male 30mg	13	12	-2.47	-3.73	3.19	3.79	1.397058295	
female 30mg	68	65	-1.86	-4.78	2.94	3.62	0.57067251	
male 60mg	13	10	-2.47	-7.63	3.19	5.75	1.880353515	
female 60mg	68	66	-1.86	-5.19	2.94	4.34	0.638688771	
male % 10mg	13	11	-2.28	-3.01	2.86	2.5	1.107066363	
female % 10mg	68	72	-2.05	-2.24	3.25	3.5	0.571715347	
male % 30mg	13	12	-2.28	-3.59	2.86	3.53	1.280222979	
female % 30mg	68	65	-2.05	-5.26	3.25	3.92	0.623258839	
male % 60mg	13	10	-2.28	-7.45	2.86	5.15	1.684635057	
female % 60mg	68	66	-2.05	-5.66	3.25	4.52	0.678565858	
male	8	3	-0.84	-7.13	6.52	5.06	4.214492193	
female	19	25	-2.95	-4.58	6.82	4.45	1.701381729	
male %	8	3	-0.93	-7.22	6.39	5.04	4.140421174	
female %	19	25	-2.66	-5.11	5.86	4.82	1.610279908	
male	3	2	5.57	-14.05	4.28	11.81	6.994301252	
female	17	20	2.14	-2.98	4.64	6.14	1.816089205	
male %	3	2	5.22	-13.46	4.84	10.93	6.796978495	
female %	17	20	1.77	-3	4.48	5.92	1.751812891	
France	97	92	-4.1	-8.16	5.85	8.53	1.059235856	
United Kingdom	98	93	-3.53	-6.42	5.31	6.12	0.827855514	
Germany	67	70	-5.56	-10.25	6.32	6.3	1.078421336	
Virtual Country	89	87	-8	-8.4	9.33	7	1.245463909	
Austria	30	29	-4.43	-5.54	6.46	6.36	1.669540818	
Belgium	24	24	-8.12	-12.62	7.22	6.34	1.96133458	
Italy	62	68	-5.98	-8.69	7.66	7.94	1.371042411	
France %	97	92	-4.08	-8.02	5.73	7.19	0.943277433	
United Kingdom %	98	93	-3.44	-6.57	4.92	6.26	0.81247391	
Germany %	67	70	-5.62	-11	6.01	6.6	1.079900891	
Virtual Country %	89	87	-7.57	-8.53	8.46	7.2	1.185395828	
Austria %	30	29	-4.71	-6.07	6.55	6.68	1.722432931	
Belgium %	24	24	-8.83	-13.49	7.8	6.49	2.071232524	
Italy %	62	68	-6.4	-9.08	7.63	7.79	1.354597401	
(Center #1) 10mg	18	19	-1.94	-2.61	2.48	3.97	1.095497011	
(Center #2) 10mg	16	16	-2.63	-1.94	3.26	3.34	1.166811896	
(Center #3) 10mg	10	11	-2	-1.36	3.37	2.87	1.361852647	
(Center #4) 10mg	18	19	-0.49	-1.58	1.79	1.91	0.609381783	
(Center #5) 10mg	10	10	-4.22	-2.97	3.67	3.16	1.531486206	
(Center #6) 10mg	9	8	-1.22	-3.25	2.77	2.55	1.297187806	
(Center #1) 30mg	18	18	-1.94	-4.11	2.48	3.03	0.922897009	
(Center #2) 30mg	16	16	-2.63	-4.31	3.26	3.94	1.2784561	
(Center #3) 30mg	10	10	-2	-6.4	3.37	4.65	1.816023128	
(Center #4) 30mg	18	15	-0.49	-4.74	1.79	3.71	0.987164598	

	ppo n	df n	ppo mean	df mean	ppo sd	df sd	SEM of dif
(Center #5) 30mg	10	9	-4.22	-3.34	3.67	2.84	1.518761342
(Center #6) 30mg	9	9	-1.22	-5.22	2.77	3.77	1.55940672
(Center #1) 60mg	18	16	-1.94	-4.09	2.48	4.05	1.137288509
(Center #2) 60mg	16	16	-2.63	-5.13	3.26	4.41	1.371032914
(Center #3) 60mg	10	10	-2	-4.3	3.37	5.48	2.034386886
(Center #4) 60mg	18	17	-0.49	-6.06	1.79	3.76	0.986314328
(Center #5) 60mg	10	10	-4.22	-7.07	3.67	5.05	1.974117524
(Center #6) 60mg	9	7	-1.22	-7.86	2.77	5.67	2.147726109
% (Center #1) 10mg	18	19	-2.11	-3.02	2.67	4.81	1.289139802
% (Center #2) 10mg	16	16	-2.95	-1.93	3.89	3.37	1.286686636
% (Center #3) 10mg	10	11	-2.13	-1.47	3.61	3.1	1.464274221
% (Center #4) 10mg	18	19	-0.54	-1.66	2.09	1.78	0.637041597
% (Center #5) 10mg	10	10	-4.02	-2.82	3.42	2.98	1.434461571
% (Center #6) 10mg	9	8	-1.39	-3.76	2.85	3.24	1.476317491
%(Center #1) 30mg	18	18	-2.11	-4.62	2.67	3.28	0.996864529
% (Center #2) 30mg	16	16	-2.95	-4.59	3.89	3.94	1.384189745
% (Center #3) 30mg	10	10	-2.13	-6.91	3.61	4.88	1.919544217
% (Center #4) 30mg	18	15	-0.54	-5.39	2.09	4.3	1.146022372
% (Center #5) 30mg	10	9	-4.02	-3.55	3.42	3.2	1.524648122
% (Center #6) 30mg	9	9	-1.39	-5.2	2.85	3.78	1.57800507
% (Center #1) 60mg	18	16	-2.11	-4.62	2.67	4.52	1.256062045
% (Center #2) 60mg	16	16	-2.95	-5.4	3.89	4.32	1.453325927
% (Center #3) 60mg	10	10	-2.13	-4.56	3.61	5.34	2.038325293
% (Center #4) 60mg	18	17	-0.54	-6.59	2.09	3.94	1.057480287
% (Center #5) 60mg	10	10	-4.02	-7.04	3.42	4.72	1.843225434
% (Center #6) 60mg	9	7	-1.39	-8.5	2.85	5.57	2.134393444
Index/df	467	463	-5.4	-8.3	7.1	7.3	0.472216244
Index/df %	467	463	-5.4	-8.6	6.8	7.2	0.459213156
Noble/df	27	28	-2.3	-4.9	6.7	4.5	1.533818546
Noble/df %	27	28	-2.1	-5.3	6	4.8	1.462437749
P003 10mg	81	83	-2	-2.2	3	3.1	0.476525792
P003 30mg	81	77	-2	-4.6	3	3.6	0.526181373
P003 60mg	81	76	-2	-5.5	3	4.6	0.616110299
P003 10mg %	81	83	-2.1	-2.3	3.2	3.4	0.515841029
P003 30mg %	81	77	-2.1	-5	3.2	3.9	0.566342969
P003 60mg %	81	76	-2.1	-5.9	3.2	4.6	0.629217123
UK 18/df	20	22	2.7	-4	4.6	7.2	1.886081797
UK 18/df %	20	22	2.3	-4	4.6	6.8	1.810156949

	95%LCL	Tx-SEM	0	Tx dif	0	Tx+SEM	95%UCL
male	-4.11152	-2.91077	0	-1.66	0	-0.40923	0.791517
female	-4.19468	-3.71239	0	-3.21	0	-2.70761	-2.22532
male %	-3.2128	-2.27102	0	-1.29	0	-0.30898	0.632803
female %	-4.64175	-4.1462	0	-3.63	0	-3.1138	-2.61825
male 10mg	-3.44214	-2.11026	0	-0.87	0	0.370257	1.702138
female 10mg	-1.14682	-0.65858	0	-0.15	0	0.358582	0.846822
male 30mg	-4.15003	-2.65706	0	-1.26	0	0.137058	1.630031
female 30mg	-4.03852	-3.49067	0	-2.92	0	-2.34933	-1.80148
male 60mg	-9.07041	-7.04035	0	-5.16	0	-3.27965	-1.24959
female 60mg	-4.58183	-3.96869	0	-3.33	0	-2.69131	-2.07817
male % 10mg	-3.02592	-1.83707	0	-0.73	0	0.377066	1.565918
female % 10mg	-1.31056	-0.76172	0	-0.19	0	0.381715	0.930562
male % 30mg	-3.95834	-2.59022	0	-1.31	0	-0.02978	1.338339
female % 30mg	-4.43159	-3.83326	0	-3.21	0	-2.58674	-1.98841
male % 60mg	-8.67339	-6.85464	0	-5.17	0	-3.48536	-1.66661
female % 60mg	-4.93999	-4.28857	0	-3.61	0	-2.93143	-2.28001
male	-15.8239	-10.5045	0	-6.29	0	-2.07551	3.243851
female	-4.96471	-3.33138	0	-1.63	0	0.071382	1.704708
male %	-15.6563	-10.4304	0	-6.29	0	-2.14958	3.076291
female %	-5.60615	-4.06028	0	-2.45	0	-0.83972	0.706149
male	-41.879	-26.6143	0	-19.62	0	-12.6257	2.639009
female	-8.67953	-6.93609	0	-5.12	0	-3.30391	-1.56047
male %	-40.311	-25.477	0	-18.68	0	-11.883	2.951039
female %	-8.20355	-6.52181	0	-4.77	0	-3.01819	-1.33645
France	-6.1361	-5.11924	0	-4.06	0	-3.00076	-1.9839
United Kingdom	-4.5126	-3.71786	0	-2.89	0	-2.06214	-1.2674
Germany	-6.80371	-5.76842	0	-4.69	0	-3.61158	-2.57629
Virtual Country	-2.84111	-1.64546	0	-0.4	0	0.845464	2.041109
Austria	-4.3823	-2.77954	0	-1.11	0	0.559541	2.1623
Belgium	-8.34422	-6.46133	0	-4.5	0	-2.53867	-0.65578
Italy	-5.39724	-4.08104	0	-2.71	0	-1.33896	-0.02276
France %	-5.78882	-4.88328	0	-3.94	0	-2.99672	-2.09118
United Kingdom %	-4.72245	-3.94247	0	-3.13	0	-2.31753	-1.53755
Germany %	-7.49661	-6.4599	0	-5.38	0	-4.3001	-3.26339
Virtual Country %	-3.28338	-2.1454	0	-0.96	0	0.225396	1.363376
Austria %	-4.73597	-3.08243	0	-1.36	0	0.362433	2.015969
Belgium %	-8.71962	-6.73123	0	-4.66	0	-2.58877	-0.60038
Italy %	-5.33501	-4.0346	0	-2.68	0	-1.3254	-0.02499
(Center #1) 10mg	-2.81717	-1.7655	0	-0.67	0	0.425497	1.477174
(Center #2) 10mg	-1.69295	-0.47681	0	0.69	0	1.856812	3.072945
(Center #3) 10mg	-2.21039	-0.72185	0	0.64	0	2.001853	3.490391
(Center #4) 10mg	-2.28439	-1.69938	0	-1.09	0	-0.48062	0.104388
(Center #5) 10mg	-1.96754	-0.28149	0	1.25	0	2.781486	4.467536
(Center #6) 10mg	-4.79489	-3.32719	0	-2.03	0	-0.73281	0.734892
(Center #1) 30mg	-3.97888	-3.0929	0	-2.17	0	-1.2471	-0.36112
(Center #2) 30mg	-4.29095	-2.95846	0	-1.68	0	-0.40154	0.930953
(Center #3) 30mg	-8.21533	-6.21602	0	-4.4	0	-2.58398	-0.58467
(Center #4) 30mg	-6.18484	-5.23716	0	-4.25	0	-3.26284	-2.31516

	95%LCL	Tx-SEM	0	Tx dif	0	Tx+SEM	95%UCL
(Center #5) 30mg	-2.32431	-0.63876	0	0.88	0	2.398761	4.084311
(Center #6) 30mg	-7.3058	-5.55941	0	-4	0	-2.44059	-0.6942
(Center #1) 60mg	-4.37909	-3.28729	0	-2.15	0	-1.01271	0.079085
(Center #2) 60mg	-5.30002	-3.87103	0	-2.5	0	-1.12897	0.30002
(Center #3) 60mg	-6.57409	-4.33439	0	-2.3	0	-0.26561	1.974092
(Center #4) 60mg	-7.50318	-6.55631	0	-5.57	0	-4.58369	-3.63682
(Center #5) 60mg	-6.99747	-4.82412	0	-2.85	0	-0.87588	1.29747
(Center #6) 60mg	-11.2464	-8.78773	0	-6.64	0	-4.49227	-2.03358
% (Center #1) 10mg	-3.43671	-2.19914	0	-0.91	0	0.37914	1.616714
% (Center #2) 10mg	-1.60776	-0.26669	0	1.02	0	2.306687	3.647762
% (Center #3) 10mg	-2.40476	-0.80427	0	0.66	0	2.124274	3.724762
% (Center #4) 10mg	-2.3686	-1.75704	0	-1.12	0	-0.48296	0.128602
% (Center #5) 10mg	-1.81369	-0.23446	0	1.2	0	2.634462	4.213694
% (Center #6) 10mg	-5.5167	-3.84632	0	-2.37	0	-0.89368	0.776698
%(Center #1) 30mg	-4.46385	-3.50686	0	-2.51	0	-1.51314	-0.55615
% (Center #2) 30mg	-4.46689	-3.02419	0	-1.64	0	-0.25581	1.18689
% (Center #3) 30mg	-8.81282	-6.69954	0	-4.78	0	-2.86046	-0.74718
% (Center #4) 30mg	-7.0962	-5.99602	0	-4.85	0	-3.70398	-2.6038
% (Center #5) 30mg	-2.74673	-1.05465	0	0.47	0	1.994648	3.686731
% (Center #6) 30mg	-7.15522	-5.38801	0	-3.81	0	-2.23199	-0.46478
% (Center #1) 60mg	-4.97188	-3.76606	0	-2.51	0	-1.25394	-0.04812
% (Center #2) 60mg	-5.41808	-3.90333	0	-2.45	0	-0.99667	0.518084
% (Center #3) 60mg	-6.71237	-4.46833	0	-2.43	0	-0.39167	1.852366
% (Center #4) 60mg	-8.12266	-7.10748	0	-6.05	0	-4.99252	-3.97734
% (Center #5) 60mg	-6.89248	-4.86323	0	-3.02	0	-1.17677	0.852476
% (Center #6) 60mg	-11.6878	-9.24439	0	-7.11	0	-4.97561	-2.53218
Index/df	-3.82554	-3.37222	0	-2.9	0	-2.42778	-1.97446
Index/df %	-4.10006	-3.65921	0	-3.2	0	-2.74079	-2.29994
Noble/df	-5.60628	-4.13382	0	-2.6	0	-1.06618	0.406284
Noble/df %	-6.06638	-4.66244	0	-3.2	0	-1.73756	-0.33362
P003 10mg	-1.13399	-0.67653	0	-0.2	0	0.276526	0.733991
P003 30mg	-3.63132	-3.12618	0	-2.6	0	-2.07382	-1.56868
P003 60mg	-4.70758	-4.11611	0	-3.5	0	-2.88389	-2.29242
P003 10mg %	-1.21105	-0.71584	0	-0.2	0	0.315841	0.811048
P003 30mg %	-4.01003	-3.46634	0	-2.9	0	-2.33366	-1.78997
P003 60mg %	-5.03327	-4.42922	0	-3.8	0	-3.17078	-2.56673
UK 18/df	-10.3967	-8.58608	0	-6.7	0	-4.81392	-3.00328
UK 18/df %	-9.84791	-8.11016	0	-6.3	0	-4.48984	-2.75209

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	DF SEM	DF 95%lcl	DF-SEM	0	DF mean	0
male	0.880973	-9.96671	-9.12097	0	-8.24	0
female	0.362903	-9.05129	-8.7029	0	-8.34	0
male %	0.639097	-8.24263	-7.6291	0	-6.99	0
female %	0.381074	-9.7369	-9.37107	0	-8.99	0
male 10mg	0.850262	-5.2345	-4.19026	0	-3.34	0
female 10mg	0.361803	-2.71913	-2.3718	0	-2.01	0
male 30mg	1.094079	-6.13805	-4.82408	0	-3.73	0
female 30mg	0.449006	-5.66005	-5.22901	0	-4.78	0
male 60mg	1.81831	-11.7433	-9.44831	0	-7.63	0
female 60mg	0.534217	-6.23707	-5.72422	0	-5.19	0
male % 10mg	0.753778	-4.68952	-3.76378	0	-3.01	0
female % 10mg	0.412479	-3.04846	-2.65248	0	-2.24	0
male % 30mg	1.019023	-5.83286	-4.60902	0	-3.59	0
female % 30mg	0.486216	-6.21298	-5.74622	0	-5.26	0
male % 60mg	1.628573	-11.1341	-9.07857	0	-7.45	0
female % 60mg	0.556374	-6.75049	-6.21637	0	-5.66	0
male	2.921392	-19.6997	-10.0514	0	-7.13	0
female	0.89	-6.41687	-5.47	0	-4.58	0
male %	2.909845	-19.7401	-10.1298	0	-7.22	0
female %	0.964	-7.0996	-6.074	0	-5.11	0
male	8.350931	-120.158	-22.4009	0	-14.05	0
female	1.372946	-5.85361	-4.35295	0	-2.98	0
male %	7.728677	-111.662	-21.1887	0	-13.46	0
female %	1.323752	-5.77065	-4.32375	0	-3	0
France	0.889314	-9.90306	-9.04931	0	-8.16	0
United Kingdom	0.634614	-7.66384	-7.05461	0	-6.42	0
Germany	0.752994	-11.7259	-11.003	0	-10.25	0
Virtual Country	0.750479	-9.87094	-9.15048	0	-8.4	0
Austria	1.181022	-7.95922	-6.72102	0	-5.54	0
Belgium	1.294147	-15.2971	-13.9141	0	-12.62	0
Italy	0.962866	-10.5772	-9.65287	0	-8.69	0
France %	0.749609	-9.48923	-8.76961	0	-8.02	0
United Kingdom %	0.649132	-7.8423	-7.21913	0	-6.57	0
Germany %	0.788851	-12.5461	-11.7889	0	-11	0
Virtual Country %	0.771921	-10.043	-9.30192	0	-8.53	0
Austria %	1.240445	-8.61094	-7.31044	0	-6.07	0
Belgium %	1.324766	-16.2305	-14.8148	0	-13.49	0
Italy %	0.944676	-10.9316	-10.0247	0	-9.08	0
(Center #1) 10mg	0.91078	-4.52348	-3.52078	0	-2.61	0
(Center #2) 10mg	0.835	-3.71976	-2.775	0	-1.94	0
(Center #3) 10mg	0.865338	-3.28809	-2.22534	0	-1.36	0
(Center #4) 10mg	0.438184	-2.50059	-2.01818	0	-1.58	0
(Center #5) 10mg	0.99928	-5.23053	-3.96928	0	-2.97	0
(Center #6) 10mg	0.901561	-5.38185	-4.15156	0	-3.25	0
(Center #1) 30mg	0.714178	-5.61679	-4.82418	0	-4.11	0
(Center #2) 30mg	0.985	-6.40948	-5.295	0	-4.31	0
(Center #3) 30mg	1.470459	-9.72641	-7.87046	0	-6.4	0
(Center #4) 30mg	0.957918	-6.79453	-5.69792	0	-4.74	0

	DF SEM	DF 95%lcl	DF-SEM	0	DF mean	0
(Center #5) 30mg	0.946667	-5.70462	-4.28667	0	-3.34	0
(Center #6) 30mg	1.256667	-7.44814	-6.47667	0	-5.22	0
(Center #1) 60mg	1.0125	-6.22145	-5.1025	0	-4.09	0
(Center #2) 60mg	1.1025	-7.2499	-6.2325	0	-5.13	0
(Center #3) 60mg	1.732928	-6.43145	-6.03293	0	-4.3	0
(Center #4) 60mg	0.911934	-8.20479	-6.97193	0	-6.06	0
(Center #5) 60mg	1.59695	-9.21479	-8.66695	0	-7.07	0
(Center #6) 60mg	2.143059	-10.0388	-10.0031	0	-7.86	0
% (Center #1) 10mg	1.10349	-5.11302	-4.12349	0	-3.02	0
% (Center #2) 10mg	0.8425	-4.10881	-2.7725	0	-1.93	0
% (Center #3) 10mg	0.934685	-3.73216	-2.40469	0	-1.47	0
% (Center #4) 10mg	0.40836	-4.02462	-2.06836	0	-1.66	0
% (Center #5) 10mg	0.942359	-5.12601	-3.76236	0	-2.82	0
% (Center #6) 10mg	1.145513	-6.06601	-4.90551	0	-3.76	0
%(Center #1) 30mg	0.773103	-6.78037	-5.3931	0	-4.62	0
% (Center #2) 30mg	0.985	-6.73479	-5.575	0	-4.59	0
% (Center #3) 30mg	1.543191	-9.07037	-8.45319	0	-6.91	0
% (Center #4) 30mg	1.110255	-7.52145	-6.50026	0	-5.39	0
% (Center #5) 30mg	1.066667	-5.85601	-4.61667	0	-3.55	0
% (Center #6) 30mg	1.26	-7.42814	-6.46	0	-5.2	0
% (Center #1) 60mg	1.13	-6.7399	-5.75	0	-4.62	0
% (Center #2) 60mg	1.08	-7.5199	-6.48	0	-5.4	0
% (Center #3) 60mg	1.688656	-6.69145	-6.24866	0	-4.56	0
% (Center #4) 60mg	0.95559	-8.72145	-7.54559	0	-6.59	0
% (Center #5) 60mg	1.492595	-9.20037	-8.5326	0	-7.04	0
% (Center #6) 60mg	2.105262	-10.6788	-10.6053	0	-8.5	0
Index/df	0.33926	-8.96495	-8.63926	0	-8.3	0
Index/df %	0.334612	-9.25584	-8.93461	0	-8.6	0
Noble/df	0.85042	-6.97388	-5.75042	0	-4.9	0
Noble/df %	0.907115	-7.3639	-6.20711	0	-5.3	0
P003 10mg	0.340269	-2.86693	-2.54027	0	-2.2	0
P003 30mg	0.410258	-5.40411	-5.01026	0	-4.6	0
P003 60mg	0.527656	-6.53421	-6.02766	0	-5.5	0
P003 10mg %	0.373198	-3.03147	-2.6732	0	-2.3	0
P003 30mg %	0.444446	-5.87111	-5.44445	0	-5	0
P003 60mg %	0.527656	-6.93421	-6.42766	0	-5.9	0
UK 18/df	1.535045	-6.03693	-5.53505	0	-4	0
UK 18/df %	1.449765	-6.04227	-5.44976	0	-4	0

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	DF+SEM	DF 95%UCL	DD SEM	PB 95%lcl	PB-SEM	0
male	-7.35903	-6.5132921	0.867897	-8.32028	-7.4679	0
female	-7.9771	-7.6287107	0.347589	-5.81127	-5.47759	0
male %	-6.3509	-5.7373705	0.745331	-7.16085	-6.44533	0
female %	-8.60893	-8.2430953	0.34862	-6.0433	-5.70862	0
male 10mg	-2.48974	-1.4454979	0.884747	-4.3977	-3.35475	0
female 10mg	-1.6482	-1.3008662	0.356527	-2.55879	-2.21653	0
male 30mg	-2.63592	-1.3219477	0.884747	-4.3977	-3.35475	0
female 30mg	-4.33099	-3.8999488	0.356527	-2.55879	-2.21653	0
male 60mg	-5.81169	-3.5166947	0.884747	-4.3977	-3.35475	0
female 60mg	-4.65578	-4.1429345	0.356527	-2.55879	-2.21653	0
male % 10mg	-2.25622	-1.3304769	0.793221	-4.00828	-3.07322	0
female % 10mg	-1.82752	-1.4315412	0.39412	-2.82248	-2.44412	0
male % 30mg	-2.57098	-1.3471439	0.793221	-4.00828	-3.07322	0
female % 30mg	-4.77378	-4.3070163	0.39412	-2.82248	-2.44412	0
male % 60mg	-5.82143	-3.7659091	0.793221	-4.00828	-3.07322	0
female % 60mg	-5.10363	-4.5695079	0.39412	-2.82248	-2.44412	0
male	-4.20861	5.43974557	2.305168	-6.29085	-3.14517	0
female	-3.69	-2.7431307	1.564615	-6.23714	-4.51462	0
male %	-4.31015	5.30006278	2.259206	-6.27217	-3.18921	0
female %	-4.146	-3.1204022	1.344376	-5.48443	-4.00438	0
male	-5.69907	92.0581855	2.471059	-5.06212	3.098941	0
female	-1.60705	-0.1063907	1.125365	-0.24567	1.014635	0
male %	-5.73132	84.7417331	2.794375	-6.80323	2.425625	0
female %	-1.67625	-0.2293539	1.08656	-0.5334	0.68344	0
France	-7.27059	-6.4169446	0.593978	-5.2642	-4.69398	0
United Kingdom	-5.78539	-5.1761557	0.536391	-4.58133	-4.06639	0
Germany	-9.49701	-8.7741317	0.772111	-7.07334	-6.33211	0
Virtual Country	-7.64952	-6.9290616	0.988978	-9.9384	-8.98898	0
Austria	-4.35898	-3.1207827	1.179429	-6.8422	-5.60943	0
Belgium	-11.3259	-9.9428564	1.473776	-11.1687	-9.59378	0
Italy	-7.72713	-6.8027818	0.972821	-7.88673	-6.95282	0
France %	-7.27039	-6.5507657	0.581793	-5.22031	-4.66179	0
United Kingdom %	-5.92087	-5.2977017	0.496995	-4.41411	-3.937	0
Germany %	-10.2111	-9.4538523	0.734238	-7.05911	-6.35424	0
Virtual Country %	-7.75808	-7.0170348	0.896758	-9.32765	-8.46676	0
Austria %	-4.82956	-3.529061	1.195861	-7.15581	-5.90586	0
Belgium %	-12.1652	-10.749517	1.592168	-12.1236	-10.4222	0
Italy %	-8.13532	-7.2284345	0.969011	-8.29926	-7.36901	0
(Center #1) 10mg	-1.69922	-0.6965198	0.584542	-3.17328	-2.52454	0
(Center #2) 10mg	-1.105	-0.1602385	0.815	-4.36713	-3.445	0
(Center #3) 10mg	-0.49466	0.55809257	1.065688	-4.41075	-3.06569	0
(Center #4) 10mg	-1.14182	-0.6594088	0.421907	-1.38015	-0.91191	0
(Center #5) 10mg	-1.97072	-0.7094705	1.160556	-6.84536	-5.38056	0
(Center #6) 10mg	-2.34844	-1.1181482	0.923333	-3.34921	-2.14333	0
(Center #1) 30mg	-3.39582	-2.6032143	0.584542	-3.17328	-2.52454	0
(Center #2) 30mg	-3.325	-2.2105209	0.815	-4.36713	-3.445	0
(Center #3) 30mg	-4.92954	-3.0735879	1.065688	-4.41075	-3.06569	0
(Center #4) 30mg	-3.78208	-2.6854687	0.421907	-1.38015	-0.91191	0

	DF+SEM	DF 95%UCL	pb SEM	PB 95%lcl	PB-SEM	0
(Center #5) 30mg	-2.39333	-1.1569813	1.160556	-6.84536	-5.38056	0
(Center #6) 30mg	-3.96333	-2.3221196	0.923333	-3.34921	-2.14333	0
(Center #1) 60mg	-3.0775	-1.931906	0.584542	-3.17328	-2.52454	0
(Center #2) 60mg	-4.0275	-2.7800754	0.815	-4.36713	-3.445	0
(Center #3) 60mg	-2.56707	-0.3798412	1.065688	-4.41075	-3.06569	0
(Center #4) 60mg	-5.14807	-4.1267868	0.421907	-1.38015	-0.91191	0
(Center #5) 60mg	-5.47305	-3.4574449	1.160556	-6.84536	-5.38056	0
(Center #6) 60mg	-5.71694	-2.6161208	0.923333	-3.34921	-2.14333	0
% (Center #1) 10mg	-1.91651	-0.7016524	0.629325	-3.43776	-2.73933	0
% (Center #2) 10mg	-1.0875	-0.1342527	0.9725	-5.02284	-3.9225	0
% (Center #3) 10mg	-0.53531	0.6126087	1.141582	-4.71244	-3.27158	0
% (Center #4) 10mg	-1.25164	-0.8020668	0.492618	-1.57933	-1.03262	0
% (Center #5) 10mg	-1.87764	-0.6882348	1.081499	-6.46652	-5.1015	0
% (Center #6) 10mg	-2.61449	-1.0512942	0.95	-3.58071	-2.34	0
%(Center #1) 30mg	-3.8469	-2.9888921	0.629325	-3.43776	-2.73933	0
% (Center #2) 30mg	-3.605	-2.4905209	0.9725	-5.02284	-3.9225	0
% (Center #3) 30mg	-5.36681	-3.4190556	1.141582	-4.71244	-3.27158	0
% (Center #4) 30mg	-4.27974	-3.0087373	0.492618	-1.57933	-1.03262	0
% (Center #5) 30mg	-2.48333	-1.0902607	1.081499	-6.46652	-5.1015	0
% (Center #6) 30mg	-3.94	-2.2944329	0.95	-3.58071	-2.34	0
% (Center #1) 60mg	-3.49	-2.2114605	0.629325	-3.43776	-2.73933	0
% (Center #2) 60mg	-4.32	-3.0980331	0.9725	-5.02284	-3.9225	0
% (Center #3) 60mg	-2.87134	-0.7399912	1.141582	-4.71244	-3.27158	0
% (Center #4) 60mg	-5.63441	-4.5642394	0.492618	-1.57933	-1.03262	0
% (Center #5) 60mg	-5.5474	-3.6635128	1.081499	-6.46652	-5.1015	0
% (Center #6) 60mg	-6.39474	-3.3486054	0.95	-3.58071	-2.34	0
Index/df	-7.96074	-7.6350508	0.328549	-6.04396	-5.72855	0
Index/df %	-8.26539	-7.9441597	0.314666	-6.01675	-5.71467	0
Noble/df	-4.04958	-3.1550833	1.289416	-4.95043	-3.58942	0
Noble/df %	-4.39289	-3.4387556	1.154701	-4.47352	-3.2547	0
P003 10mg	-1.85973	-1.5330724	0.333333	-2.65333	-2.33333	0
P003 30mg	-4.18974	-3.7958942	0.333333	-2.65333	-2.33333	0
P003 60mg	-4.97234	-4.4657939	0.333333	-2.65333	-2.33333	0
P003 10mg %	-1.9268	-1.568531	0.355556	-2.79689	-2.45556	0
P003 30mg %	-4.55555	-4.1288854	0.355556	-2.79689	-2.45556	0
P003 60mg %	-5.37234	-4.8657939	0.355556	-2.79689	-2.45556	0
UK 18/df	-2.46495	-0.8076983	1.028591	0.547133	1.671409	0
UK 18/df %	-2.55024	-0.9850484	1.028591	0.147133	1.271409	0

APPEARS THIS WAY
ON ORIGINAL

	PB mean	0	PB+SEM	PB 95%UCL
male	-6.58	0	-5.6921	-4.83972138
female	-5.13	0	-4.78241	-4.44872564
male %	-5.7	0	-4.95467	-4.23915218
female %	-5.36	0	-5.01138	-4.67670405
male 10mg	-2.47	0	-1.58525	-0.54230233
female 10mg	-1.86	0	-1.50347	-1.16120636
male 30mg	-2.47	0	-1.58525	-0.54230233
female 30mg	-1.86	0	-1.50347	-1.16120636
male 60mg	-2.47	0	-1.58525	-0.54230233
female 60mg	-1.86	0	-1.50347	-1.16120636
male % 10mg	-2.28	0	-1.48678	-0.55171933
female % 10mg	-2.05	0	-1.65588	-1.27752403
male % 30mg	-2.28	0	-1.48678	-0.55171933
female % 30mg	-2.05	0	-1.65588	-1.27752403
male % 60mg	-2.28	0	-1.48678	-0.55171933
female % 60mg	-2.05	0	-1.65588	-1.27752403
male	-0.84	0	1.465168	4.61085251
female	-2.95	0	-1.38538	0.33713732
male %	-0.93	0	1.329206	4.41216987
female %	-2.66	0	-1.31562	0.16443178
male	5.57	0	8.041059	16.2021168
female	2.14	0	3.265365	4.52566732
male %	5.22	0	8.014375	17.2432349
female %	1.77	0	2.85656	4.07340293
France	-4.1	0	-3.50602	-2.93580409
United Kingdom	-3.53	0	-2.99361	-2.47867364
Germany	-5.56	0	-4.78789	-4.04666266
Virtual Country	-8	0	-7.01102	-6.06160308
Austria	-4.43	0	-3.25057	-2.01779504
Belgium	-8.12	0	-6.64622	-5.07126553
Italy	-5.98	0	-5.00718	-4.07327089
France %	-4.08	0	-3.49821	-2.93968503
United Kingdom %	-3.44	0	-2.943	-2.4658897
Germany %	-5.62	0	-4.88576	-4.18089281
Virtual Country %	-7.57	0	-6.67324	-5.81235392
Austria %	-4.71	0	-3.51414	-2.25418847
Belgium %	-8.83	0	-7.23783	-5.53635335
Italy %	-6.4	0	-5.43099	-4.5007385
(Center #1) 10mg	-1.94	0	-1.35546	-0.70672329
(Center #2) 10mg	-2.63	0	-1.815	-0.89286755
(Center #3) 10mg	-2	0	-0.93431	0.41075461
(Center #4) 10mg	-0.49	0	-0.06809	0.4001473
(Center #5) 10mg	-4.22	0	-3.05944	-1.59463815
(Center #6) 10mg	-1.22	0	-0.29667	0.90921186
(Center #1) 30mg	-1.94	0	-1.35546	-0.70672329
(Center #2) 30mg	-2.63	0	-1.815	-0.89286755
(Center #3) 30mg	-2	0	-0.93431	0.41075461
(Center #4) 30mg	-0.49	0	-0.06809	0.4001473

	PB mean	0	PB+SEM	PB 95%UCL
(Center #5) 30mg	-4.22	0	-3.05944	-1.59463815
(Center #6) 30mg	-1.22	0	-0.29667	0.90921186
(Center #1) 60mg	-1.94	0	-1.35546	-0.70672329
(Center #2) 60mg	-2.63	0	-1.815	-0.89286755
(Center #3) 60mg	-2	0	-0.93431	0.41075461
(Center #4) 60mg	-0.49	0	-0.06809	0.4001473
(Center #5) 60mg	-4.22	0	-3.05944	-1.59463815
(Center #6) 60mg	-1.22	0	-0.29667	0.90921186
% (Center #1) 10mg	-2.11	0	-1.48067	-0.78223838
% (Center #2) 10mg	-2.95	0	-1.9775	-0.87716404
% (Center #3) 10mg	-2.13	0	-0.98842	0.4524404
% (Center #4) 10mg	-0.54	0	-0.04738	0.499334
% (Center #5) 10mg	-4.02	0	-2.9385	-1.57347752
% (Center #6) 10mg	-1.39	0	-0.44	0.80070535
%(Center #1) 30mg	-2.11	0	-1.48067	-0.78223838
% (Center #2) 30mg	-2.95	0	-1.9775	-0.87716404
% (Center #3) 30mg	-2.13	0	-0.98842	0.4524404
% (Center #4) 30mg	-0.54	0	-0.04738	0.499334
% (Center #5) 30mg	-4.02	0	-2.9385	-1.57347752
% (Center #6) 30mg	-1.39	0	-0.44	0.80070535
% (Center #1) 60mg	-2.11	0	-1.48067	-0.78223838
% (Center #2) 60mg	-2.95	0	-1.9775	-0.87716404
% (Center #3) 60mg	-2.13	0	-0.98842	0.4524404
% (Center #4) 60mg	-0.54	0	-0.04738	0.499334
% (Center #5) 60mg	-4.02	0	-2.9385	-1.57347752
% (Center #6) 60mg	-1.39	0	-0.44	0.80070535
Index/df	-5.4	0	-5.07145	-4.75604432
Index/df %	-5.4	0	-5.08533	-4.78325371
Noble/df	-2.3	0	-1.01058	0.35043346
Noble/df %	-2.1	0	-0.9453	0.2735225
P003 10mg	-2	0	-1.66667	-1.34666667
P003 30mg	-2	0	-1.66667	-1.34666667
P003 60mg	-2	0	-1.66667	-1.34666667
P003 10mg %	-2.1	0	-1.74444	-1.40311111
P003 30mg %	-2.1	0	-1.74444	-1.40311111
P003 60mg %	-2.1	0	-1.74444	-1.40311111
UK 18/df	2.7	0	3.728591	4.85286694
UK 18/df %	2.3	0	3.328591	4.45286694

Dexfenfluramine for the Treatment of Obesity

Interneuron Pharmaceuticals, Inc.

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Dexfenfluramine for the Treatment of Obesity

- Approved and marketed in 65 countries
  - First approval in 1985
  - Estimated >10,000,000 patients treated worldwide
- Dexfenfluramine is the d-isomer of the approved drug, fenfluramine
  - Estimated >30,000,000 patients treated worldwide with fenfluramine
- NDA included > 4500 patients and subjects
  - IND opened October 1991
  - NDA submitted May 1993

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Dexfenfluramine Agenda: September 28, 1995

I. Introduction	Glenn L. Cooper, M.D.
II. Obesity: Need for Treatment	Theodore VanItallie, M.D. JoAnn Manson, M.D., Dr.Ph. George Bray, M.D.
III. Mechanism of Action	Richard J. Wurtman, M.D.
IV. Neurochemical Effects of Large Doses	Robert Y. Moore, M.D., Ph.D.
V. Efficacy & Safety	Bobby W. Sandage, Jr., Ph.D.

Dexfenfluramine Agenda: September 28, 1995

VI. Special Safety & Overall Risk/Benefit	Gerald A. Faich, M.D., MPH
VII. Lack of Abuse Potential	Theodore J. Cicero, Ph.D.
VIII. Conclusion	Louis Lasagna, M.D.

Theodore VanItallie, M.D.

Professor Emeritus of Medicine at
Columbia University College of
Physicians and Surgeons
New York

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Obesity

Need for Treatment

6

Criteria for "Obesity"

	BMI (kg/m^2)	
	Men	Women
National Center for Health Statistics, 1994*	≥ 27.8	≥ 27.3
NIH Consensus Conference, 1985*	≥ 27.2	≥ 26.9
NAASO, 1995	≥ 27	≥ 27
IOM, 1994	≥ 27	≥ 27
National Institute of Diabetes, Digestive & Kidney Diseases, 1993	≥ 25**	≥ 25**
	≥ 27	≥ 27

* "overweight" is used instead of "obesity"

** ≥ 25 for those ≤ 34 years old

Increasing Prevalence of Overweight/Obesity- US Residents Aged 20-74 years

	Prevalence of Obesity (%)	
	NHANES II	NHANES III, phase I
	1976-1980	1988-1991
All subjects	25.4	33.3
Men	24.1	31.7
Women	26.5	34.9

Kuczmarski et al., 1994; VanItallie, 1985

Distribution of Body Mass Indices (BMIs) Among US Resident Population 20-74 Years of Age

BMI Range (kg/m^2)	Percent of Population[1]	Number of Persons in BMI Range (in millions)[2]
<25	48	79.3
25 to <27	15	24.8
27 to <30	16	26.4
30 to <35	14	23.1
35 to <40	4	6.6
≥40	3	5.0

Number with BMI ≥27 (23% overweight): 61.1 million
Number with BMI ≥30 (36% overweight): 34.7 million
Number with BMI ≥35 (59% overweight): 11.6 million

[1]NHANES III, phase 1, NCHS, 1995
[2]In 1991, in the US, there were 165.2 million men and women of all races 20-74 years of age (from: Health United States 1993, DHHS Pub. No. (PHS)94-1232)

Obesity and Excess Deaths

- From information currently available, one can estimate the number of deaths from certain diseases that could be attributed to obesity in the US in 1993:

Attributable to Obesity	
Cause-Specific deaths	Deaths from all causes
171,490 CHD deaths	
39,679 diabetes deaths	292,410
53,087 cancer deaths	
10,000 cerebrovascular deaths	

- An appreciable, but as yet unquantified, proportion of deaths arising from such conditions as non-CHD forms of heart disease and obstructive sleep apnea (examples) may be attributable to overweight

Excess Illnesses Attributable to Obesity

Disease	Number of Extant Cases (millions)	Overweight-attributable (millions)
Hypertension	43.2	8.6
NIDDM	11.7	9.4
Coronary Heart Disease	7.2	2.5
Cerebrovascular Disease	3.4	0.2
Totals	65.5	20.7

JoAnn E. Manson, M.D., Dr.PH

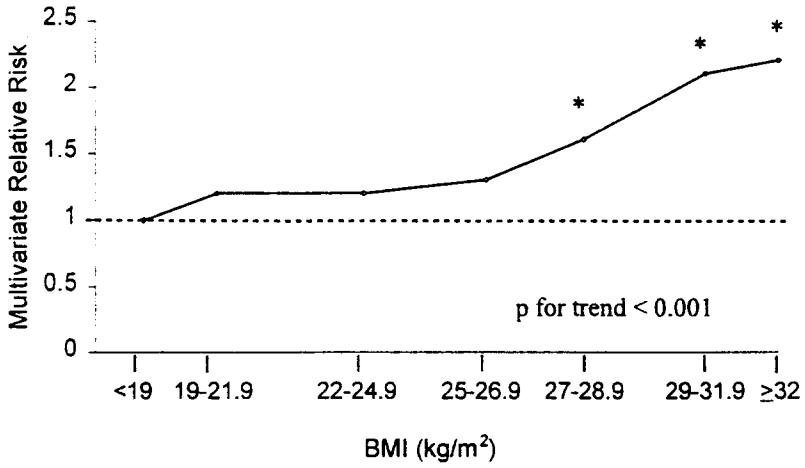
Co-Director of Women's Health and
Director of Endocrinology in the
Division of Preventive Medicine

Brigham & Women's Hospital

Associate Professor of Medicine

Harvard Medical School

BMI and All Cause Mortality Risk, Women
Never Smokers 1980-1992 with Prior Stable Weight



* $p < 0.05$

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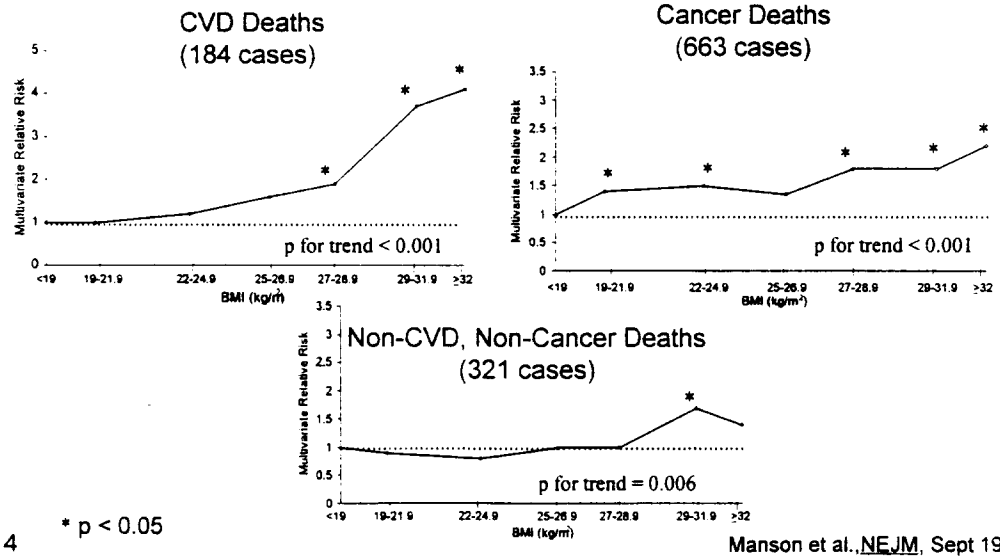
Manson et al., NEJM, Sept 1995

Cause Specific Mortality, Women
Never Smokers 1980-1992



* $p < 0.05$

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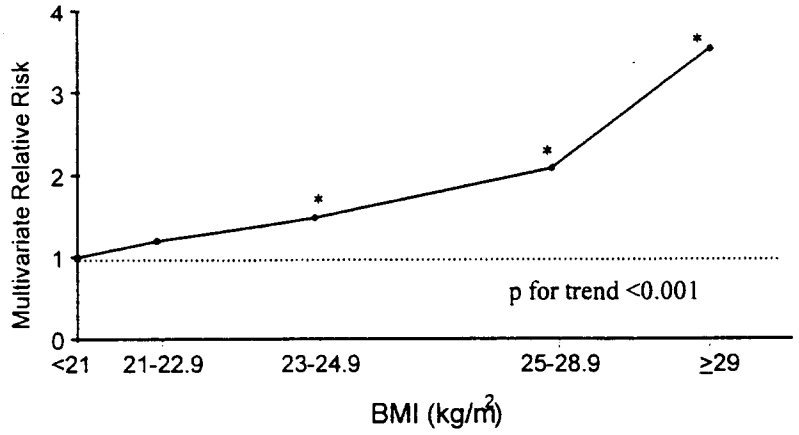
Manson et al., NEJM, Sept 1995

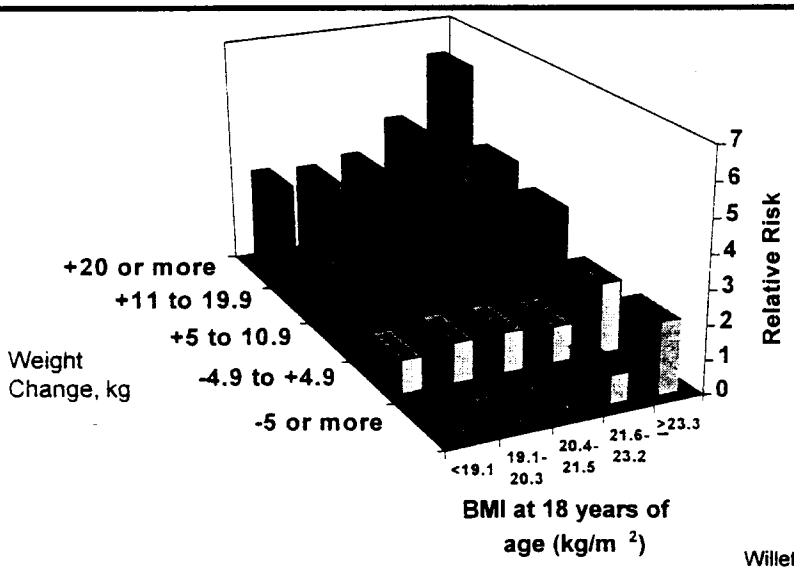
BMI and Risk of Coronary Heart Disease



* $p < 0.05$

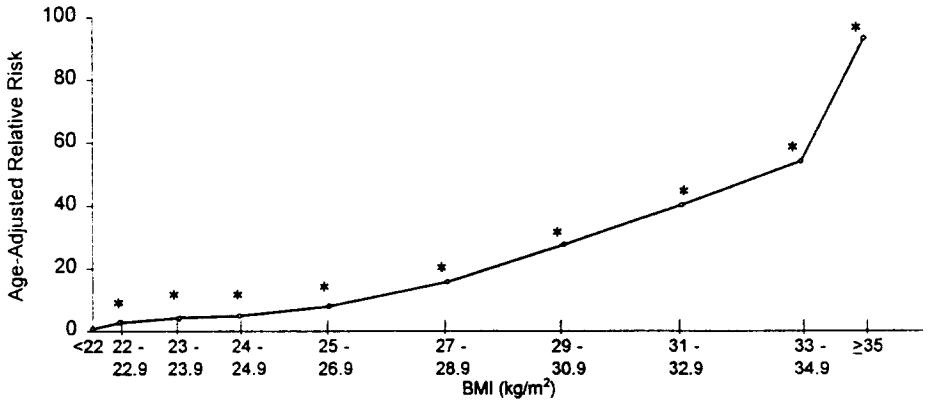
Willett et al., JAMA 1995

BMI and Risk of Coronary Heart Disease



Willett et al., JAMA 1995

BMI and Risk of NIDDM



* $p < 0.05$

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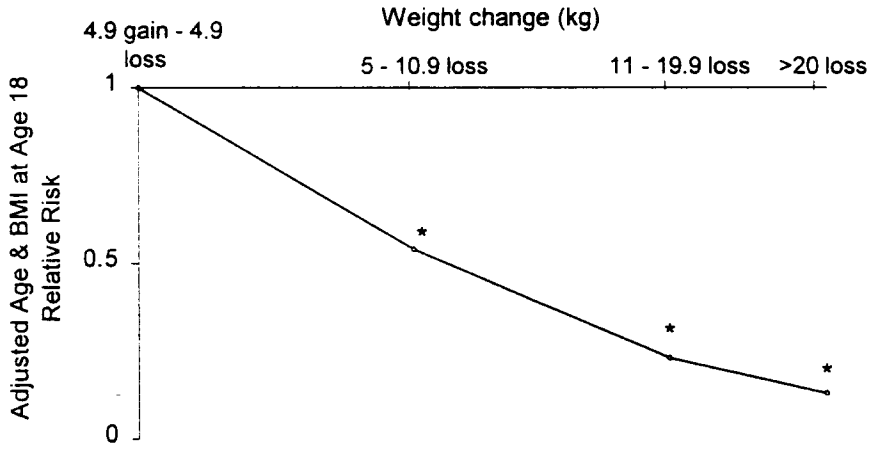
Colditz et al., Ann Int Med, 1995

Weight Loss and Risk of Diabetes



* $p < 0.05$

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Colditz et al., Ann Int Med, 1995

Intentional Weight Loss and Mortality Risk (Never-Smoking US White Women Aged 40-64 yrs)

- 28,388 obese women with no preexisting illness
- Intentional weight loss of ≥ 20 lb (9.1 kg) that occurred within the previous year was associated with :

25% reduction in all-cause, cardiovascular and cancer mortality

Williamson et al., Am J Epidemiol, 1995

Intentional Weight Loss and Mortality Risk (Never-Smoking US White Women Aged 40-64 yrs)

- 15,069 women (BMI ≥ 27 kg/m^2) with obesity and co-morbid conditions (CHD, hypertension, stroke, diabetes, cancer, or cirrhosis)
- Intentional weight loss of any amount was associated with:
  - 20% reduction in all-cause mortality
  - 30-40% reduction in diabetes-associated mortality
  - 40-50% reduction in mortality from obesity-related cancer

Williamson et al., Am J Epidemiol, 1995

Mortality Ratios Similar to those Observed in Men

- Harvard University Alumni Study
- American Cancer Society Study
- Seventh Day Adventist Study
- Framingham 30 year Follow-up Study

George A. Bray, M.D.

Executive Director
Pennington BioMedical Research Center in Baton Rouge
Professor of Medicine
LSU Medical Center

Obesity Increases Health Costs

Disease	Cost Attributable to Obesity (in billions)
Cardiovascular disease	$ 22.2
Musculoskeletal disease	$ 17.0
Diabetes	$ 11.3
Gallbladder disease	$ 2.3
Cancer	$ 1.9
Hypertension	$ 1.5
Total (or 7.8% of U.S. Health care costs)	$ 56.2

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Metabolic Benefits of Weight Loss

Measure	Effect of 20 lb loss	Risk of CHD
Cholesterol	⇩ 10 mg/dl	⇩ 10%
HDL-cholesterol	⇧ 3 mg/dl	⇩ 6%
Blood pressure (diastolic)	⇩ 5 mmHg	⇩ 15%

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Adapted from Grundy, 1995

Obesity has Many Causes

- Hypothalamic injury
- Endocrine disease
- High fat diet
- Sedentary life style
- Drug-induced
- Genetic

Obesity has ManyTreatments

- Dieting
- Exercise
- Behavior modification
- Appetite suppressants
  - Drugs to lower food intake
  - Drugs to modulate metabolism
  - Drugs to increase expenditure
- Surgery

Recidivism is Common

Drop-outs in Trials	20-80%
Time to regain weight	
1 year	30-60%
5 years	> 95%

NIH Consensus Conference on Methods of Voluntary Weight Loss, 1985

Summary

- Obesity is a chronic disease which is increasing in prevalence
- Obesity increases risk of mortality and morbidity
- Obesity increases health costs
- Intentional weight reduction of 5-10% significantly reduces risk
- Obesity has many causes and many treatments
- Treatments don't work when not used and recidivism is thus common

Richard J. Wurtman, M.D.

Cecil B. Green Distinguished Professor
Department of Brain & Cognitive Sciences
Director of the Clinical Research Center
Massachusetts Institute of Technology

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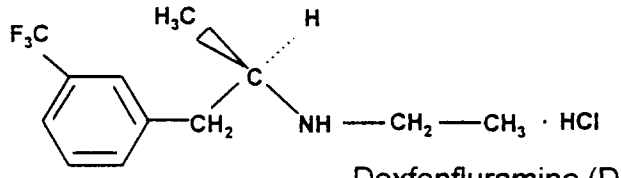
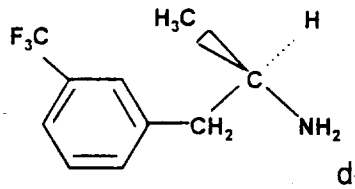
Dexfenfluramine and d-Norfenfluramine



Dexfenfluramine (DF)



d-Norfenfluramine (dNF)

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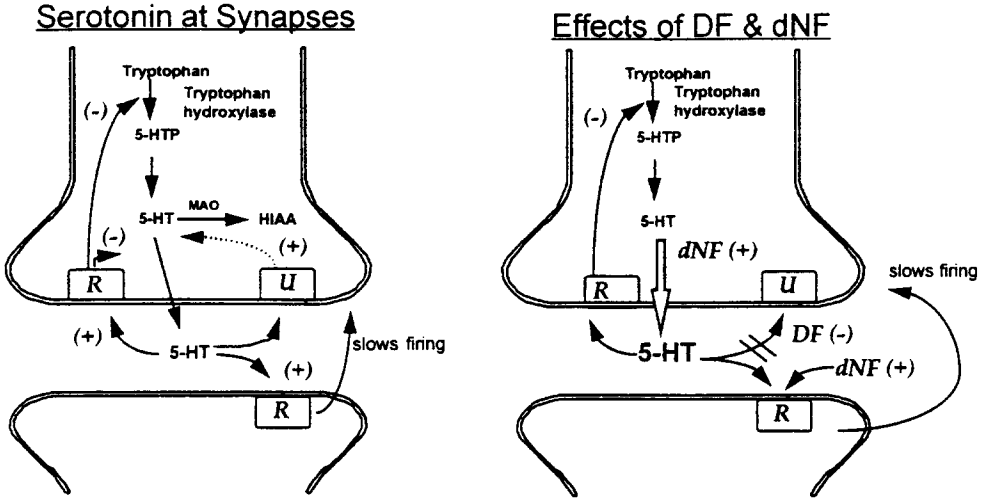
Pharmacologic Effects of Dexfenfluramine and d-Norfenfluramine



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Comparative Pharmacology

- Dexfenfluramine
  - Serotonin reuptake inhibitor
  - Serotonin releaser (dNF)
  - Serotonin agonist (dNF)
- Sympathomimetics
  - Norepinephrine releaser
  - Dopamine releaser
  - Adrenergic agonist

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Dexfenfluramine: Human Pharmacokinetics and Metabolism

- Absorption
  - Bioavailability 68.4 ±19.9%
  - T_{max} = 2.8 ± 0.9 to 5.2 ± 1.7 hours
- Distribution
  - Protein binding = 36%
  - Vd = 836.6 L
- Metabolism
  - Metabolized in the liver
  - Dealkylation to d-norfenfluramine (active metabolite)
- Elimination
  - Clearance = 691.9 ml/min
  - No accumulation
  - $t_{1/2}$ = 17.9 ± 7.9 to 20.5 ± 11.3 hours

Effects of Serotonin and Dexfenfluramine on Food Intake and Energy Utilization

- ⇧ Serotonin
  - Increases satiety
  - Suppresses carbohydrate craving
  - Increases basal energy utilization
- Dexfenfluramine
  - Reduces daily caloric intake 400-600 kcal/day
  - Increases basal energy expenditure 100 kcal/day

Animal Models in Which Dexfenfluramine Reduces Food Intake

- Acute food deprivation
- Feeding schedules
- Runway performance
- Drug-induced feeding
  - Insulin
  - 2-DG
  - Muscimol
  - 8-OH-DPAT
  - Norepinephrine
- Dessert eating
- Tail pressure
- Ad libitum feeding
- Ob/Ob mouse
- *fa/fa* rat

Rowland & Carlton, Clin Neuropharmacol, 1988
Rowland, Pharm Biochem Behav, 1994

Effect of Dexfenfluramine on Meal and Snack Consumption in Humans

Study	Subjects	Dosing	% decreased intake
Silverstone, 1987	Normal	1 day	40%
Goodall, 1988	Normal	1 day	25%
Blundell, 1988	Normal	1 day	11%
Hill, 1986	Normal	5 days	18%
Hill, 1990	Obese	3 days	11%
MIT-296	Obese	8 days	23%
MIT-124	Obese	3 mo	22%
Anderson, 1989	Obese	6 mo	13%

Effect of Dexfenfluramine on Meal and Snack Consumption

		Placebo	Dexfenfluramine	% Reduction
Meals:	kcal.	1940 ± 94	1630 ± 92*	16*
	Protein (g)	104 ± 6.1	93 ± 5.2	10
	CHO (g)	121 ± 8.4	94 + 6.7*	23*
Snacks:	kcal.	707 ± 97	414 ± 46*	41*
	Protein (number/d)	0.7 ± 0.2	0.5 ± 0.2	28
	CHO (number/d)	5.8 ± 0.8	3.4 ± 0.4*	41*

Dexfenfluramine (15 mg bid) or placebo x 8 days

*p<0.01 significant difference from placebo group

Wurtman et al., Int J Eating Disorders , 1985

Summary

- Dexfenfluramine:
  - Increases serotoninergic neurotransmission and is not sympathomimetic
  - Enhances satiety and reduces daily caloric intake

Robert Y. Moore, M.D., Ph.D.

Professor of Psychiatry, Neurology and Neuroscience

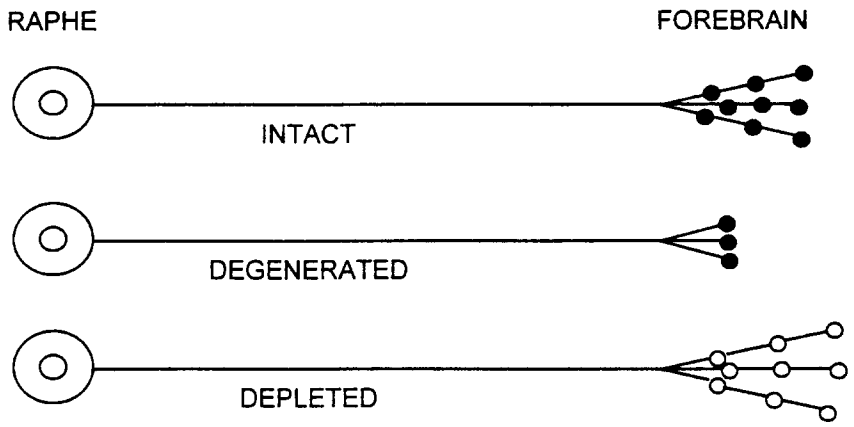
Director of the Center for Neurosciences

University of Pittsburgh

Overview

- Acute decreases in brain serotonin content have been observed following high dose dexfenfluramine administration in animals; prolonged decreases have been reported.
- All currently available evidence indicates that the reduction in serotonin content observed with high dose dexfenfluramine administration represents a pharmacologic, not a neurotoxic effect.
- No study to date has reported any finding that could be interpreted as a histologic lesion.

Serotonin Neurons



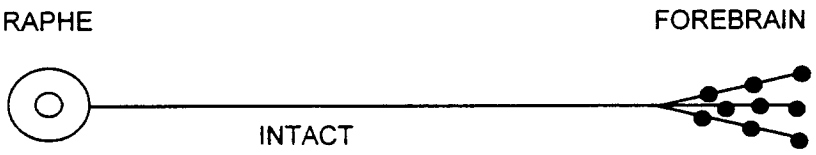
Serotonin Neuron Cell Body

Photomicrograph of serotonin neuron cell body and axonal plexus in color

The Depletion Explanation Has Two Principal Supports

- Depletion of serotonin is not associated with indices of neuron damage
- Retrograde transport is normal in the face of serotonin depletion

Serotonin Neuron



Comparison of the Effects of Dexfenfluramine with Known Neurotoxins in Tests for Neuronal Damage

	Neurotoxins			
Measure	PCA	5,7-DHT	MDMA	DF
Argyrophilia	+	+	+	-
Gliosis	+	+	+	-
Reduction in Retrograde Transport	+	+	NT	-

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Duration of Effect of Dexfenfluramine on Cortical Serotonin Levels

	Time After Discontinuation of Dosing		
Daily Dose[a] (mg/kg)	1 Week	13 Weeks	6 Months
2	99 ± 11	105 ± 37	102 ± 42
4	83 ± 7*	78 ± 18	112 ± 31
Pair-fed cont	97 ± 8	121 ± 25	86 ± 19
8	57 ± 19*	87 ± 15	92 ± 34
Pair-fed cont	105 ± 10	98 ± 46	80 ± 23
16	35 ± 7*	49 ± 11*	82 ± 19
Pair-fed cont	97 ± 14	126 ± 21	78 ± 12

46 [a] 21 day oral dosing *$p \leq 0.05$ vs. pair-fed control; Values shown as percent of pair-fed control

Effects of Dexfenfluramine on Brain Serotonin Content and Paroxetine Binding - Long-Term Mouse Study

Parameter	At End of 2 yrs of Treatment	Three Months After End of 2 yrs of Treatment
Serotonin Content[a]	109 ± 6 (n=10)	100 ± 8 (n=9)
Paroxetine Binding[a]	95 ± 8 (n=5)	130 ± 5 (n=5)
DF + dNF (μM) (brain)	51	0

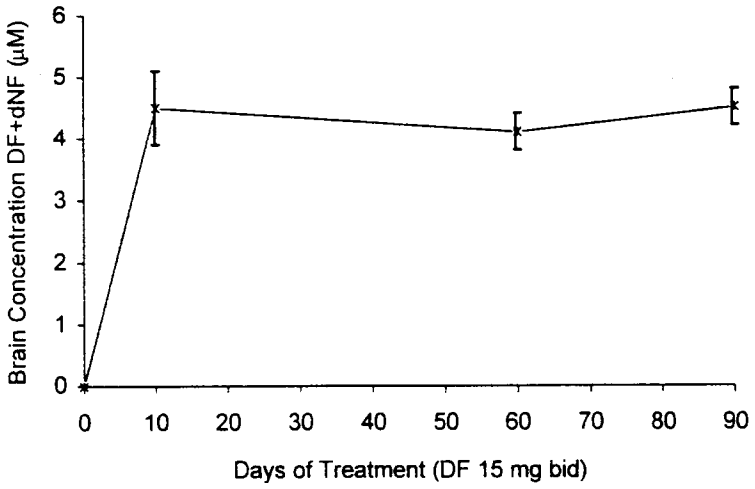
DF (27 mg/kg/day) in feed for 106 weeks

[a]Expressed as percent control values

Effect of Brain Concentrations of Dexfenfluramine and d-Norfenfluramine on Brain 5-HT Levels in Various Species

- Acute effects (2 hrs post treatment) of DF on brain 5-HT levels are related to brain DF + dNF concentrations in rats, mice and primates
- Species differences are pharmacokinetic

Brain Concentration of DF+dNF In Obese Patients



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Conclusions

- Acute high dose dexfenfluramine (DF) administration produces reversible changes in brain serotonin content in animals without evidence of neuronal damage
- High dose DF administration to mice for up to 2 years produces no alteration of brain serotonin or serotonin transporter content
- Human brain DF + dNF concentrations are stable and do not accumulate with extended treatment
- Brain concentrations achieved in the two year mouse study with high dose DF administration (a no effect level with respect to serotonin content) predict <u>at least</u> a 10-fold margin of safety

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Bobby W. Sandage, Jr., Ph.D.

Senior Vice President
Research and Development
Interneuron Pharmaceuticals, Inc.

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Dexfenfluramine: Efficacy and Safety

- Overview of the Database
- Efficacy
  - Placebo-controlled trials
  - Open-label, long-term trial
  - Patients with co-morbid conditions
  - Response predictors
- Safety
  - Extent of exposure
  - Adverse events
  - Discontinuations
  - Post-marketing experience

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Clinical Trial Experience

18	Double-blind, placebo-controlled weight loss trials
1	Dose ranging weight loss trial -together enrolled 2,342 patients
22	Other trials (pharmacology, pharmacokinetics, obese patients with co-morbid conditions)
Total	NDA safety database: 4,596 patients and subjects

Scope of the Database

	DF(15 mg bid)	Placebo
Placebo controlled		
-US	405	382
-European	754	756
Uncontrolled	1966	
All patients	3125	1138

NDA Obese Patient Database: Demographics

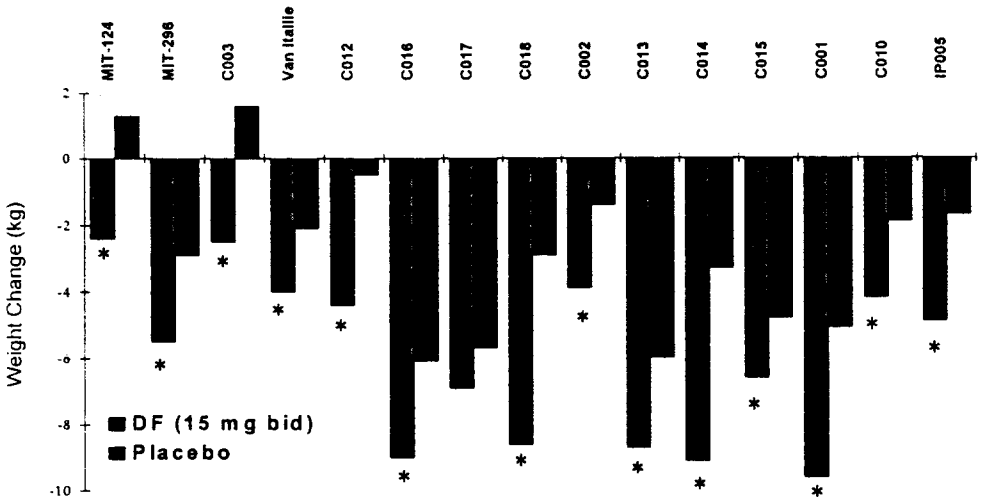
	DF (15 mg bid)	Placebo
n	3051	1138
Female (%)	84.5%	81.5%
Age Range (yrs)	41.3±12	40.8±12
Baseline Weight (kg)	87.9±17	94.3±18
Body Mass Index (kg/m^2)	32.8±5	34.6±6
% Ideal Body Weight	144.3±23	152.8±25

74 patients exposed to DF in more than one trial are counted only once

Dose Ranging and Long Term Studies

- IP92-003: US Double-Blind, Placebo-Controlled, Dose-Ranging, Multicenter, 3 Months; n=339
- Noble: US Double-Blind, Placebo-Controlled, Single-Center, 6 Months; n=60
- UK 18: European Double-Blind, Placebo-Controlled, Single-Center, 6 Months; n=45
- INDEX: European Double-Blind, Placebo-Controlled, Multicenter, 12 Months; n=1047

Other Placebo-Controlled Weight Loss Trials



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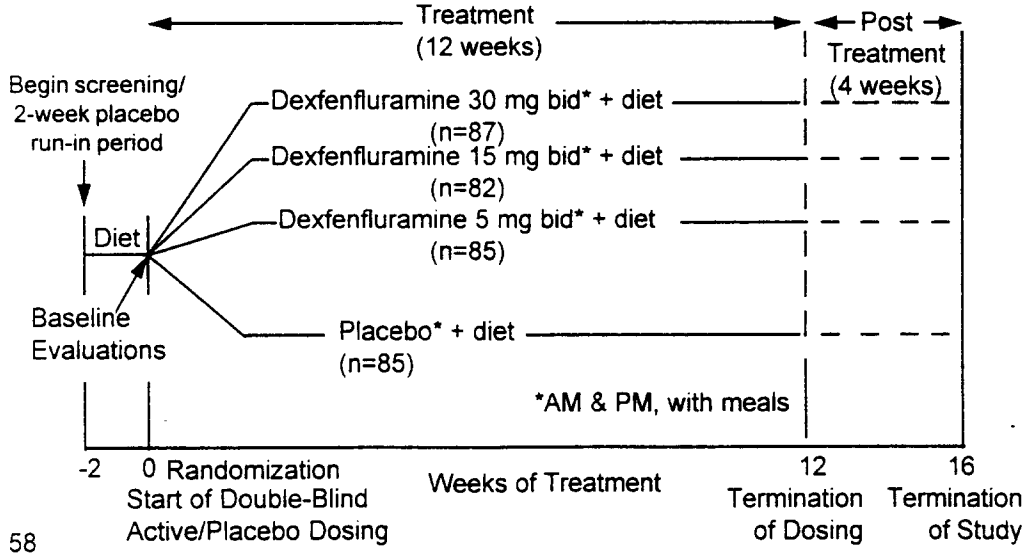
LOCF

IP92-003 STUDY SCHEMA



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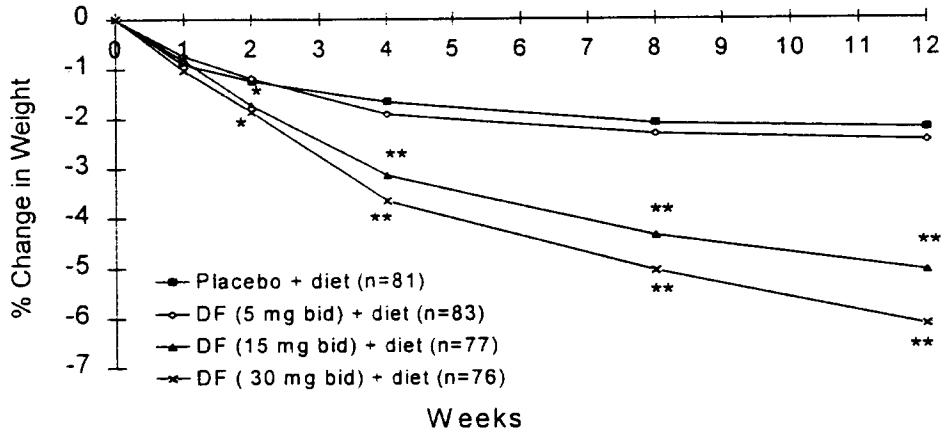
Dose-Response Effects of Dexfenfluramine - IP92-003



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* $p < 0.04$, ** $p < 0.0001$

LOCF

Adverse Events - IP92-003

Adverse Event	Placebo (n=85)	DF 5 mg bid (n=85)	DF 15 mg bid (n=82)	DF 30 mg bid (n=87)
Diarrhea	9.4%	10.6%	22%*	32.9%*
Asthenia	4.7%	9.4%	14.6%	27.6%*
Dry mouth	4.7%	5.9%	13.4%*	26.4%*
Somnolence	2.4%	7.1%	8.5%	18.4%*
Dizziness	2.4%	1.2%	7.3%	20.7%*
Thinking abnormal	1.2%	2.4%	1.2%	10.3%*
Discontinuations due to AEs	7.1%	4.7%	8.5%	16.1%

* $p < 0.05$

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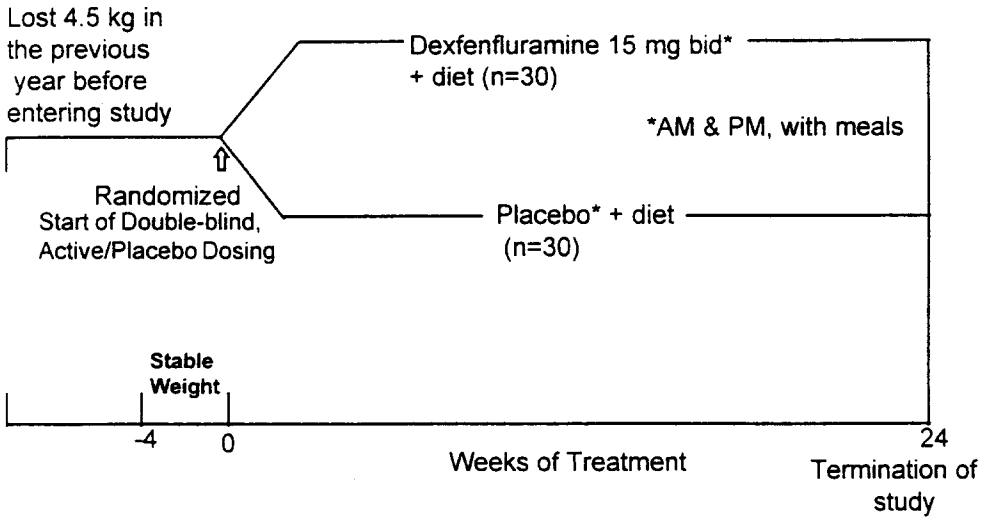
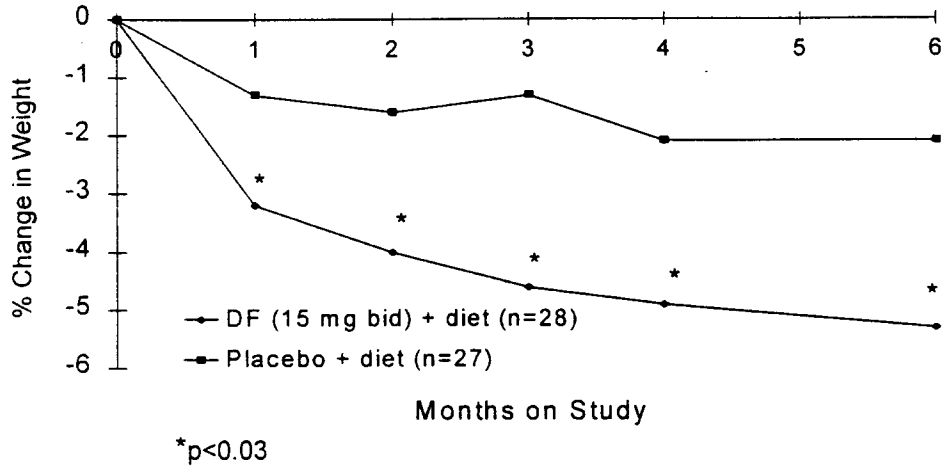
NOBLE - STUDY SCHEMA



Demographic and Background Data - Noble

Parameter	DF Mean (±sd)	Placebo Mean (±sd)
n	30	30
Males/Females	4/26	9/21
Age (yrs)	39.4 (±9.4)	43.1 (±10.5)
Height (cm)	165.5 (±8.0)	168.4 (±8.5)
Baseline Weight (kg)	93.2 (±20.9)	100.2 (±18.2)
Body Mass Index (kg/m^2)	34.0 (±7.2)	35.3 (±6.0)
Percent Ideal Weight MLIC	150.8% (±32.8)	157.1% (±27.4)

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



*p<0.03

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LOCF

Effect of Dexfenfluramine on % Weight Loss from Baseline Compared to Placebo - Noble

% of Patients with % Weight Loss at Endpoint (6 mo)

	≥ 5%			≥ 10%		
Analysis	DF	Placebo	p-Value	DF	Placebo	p-Value
LOCF	46%	19%	.027	21%	7%	.140
Completers	63%	22%	.006	32%	9%	.060

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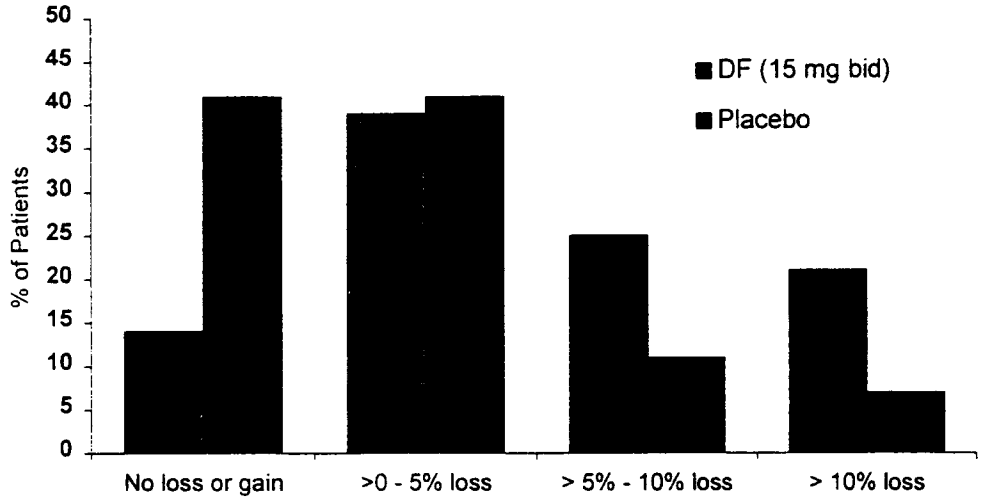
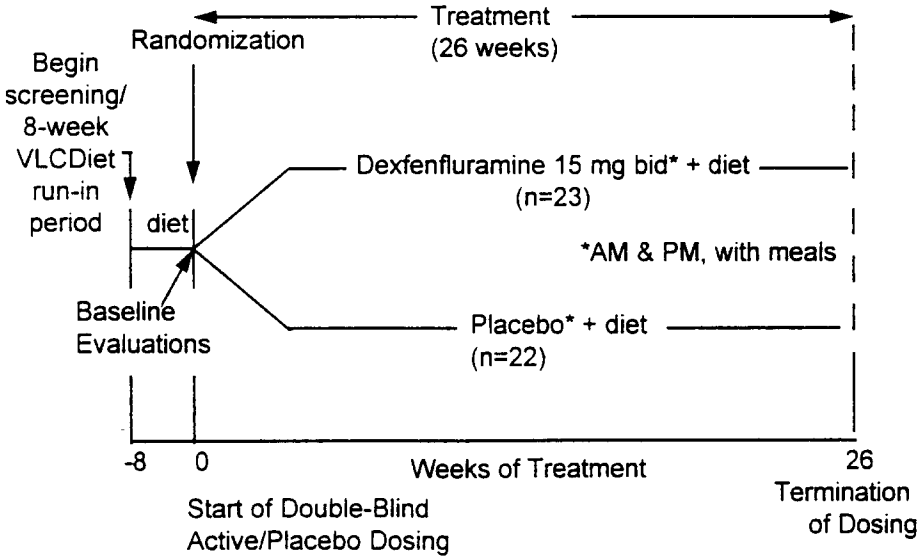
Effect of Dexfenfluramine on % Weight Loss from Baseline by Category Compared to Placebo - Noble



65 $p \leq 0.078$ difference between groups LOCF

UK 18 - STUDY SCHEMA



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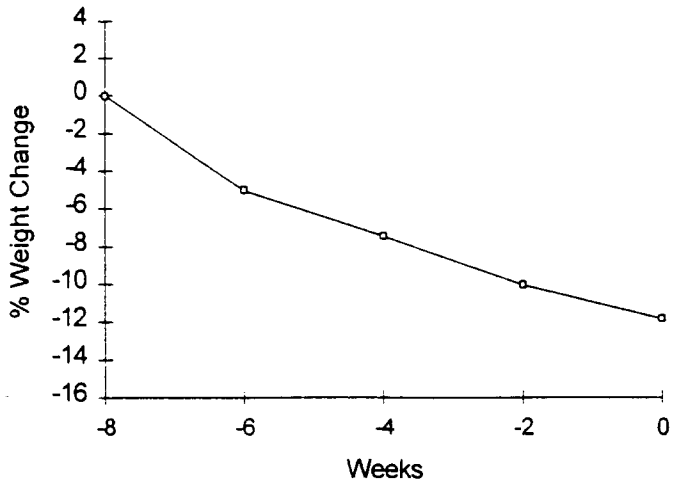
Demographic and Background Data - UK 18

Parameter	DF Mean (±sd)	Placebo Mean (±sd)
n	23	22
Males/Females	2/21	4/18
Age (yrs)	39.3 (±12.9)	31.9 (±10.3)*
Height (cm)	164.8 (±7.4)	168.0 (±9.6)
Baseline Weight (kg)	107.9 (±21.2)	107.3 (±21.7)
Body Mass Index (kg/m^2)	39.7 (±7.4)	37.8 (±6.1)
Percent Ideal Weight MLIC	151.5% (±21.4)	152.6% (±19.5)

67 * $p < 0.05$

Effect of VLCD in Patients prior to Randomization - UK 18



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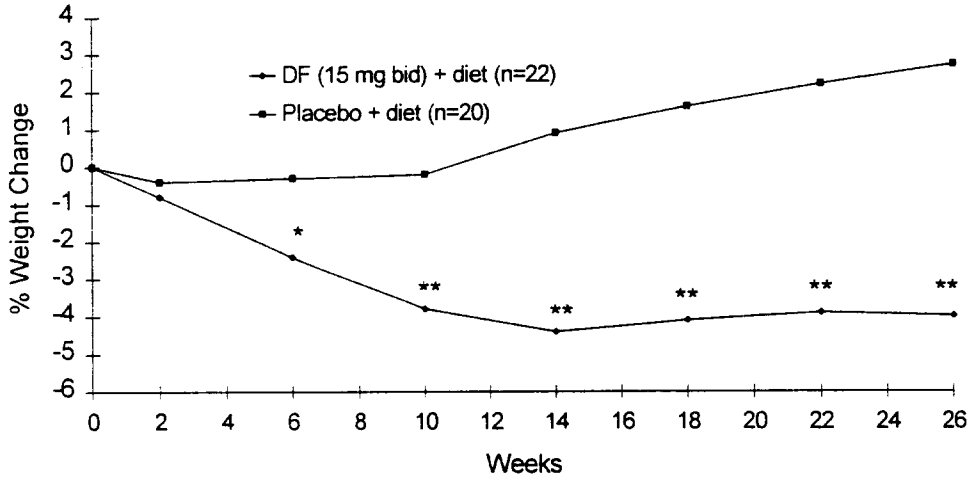
Effect of Dexfenfluramine vs. Placebo in Patients with Previous Weight Loss- UK 18



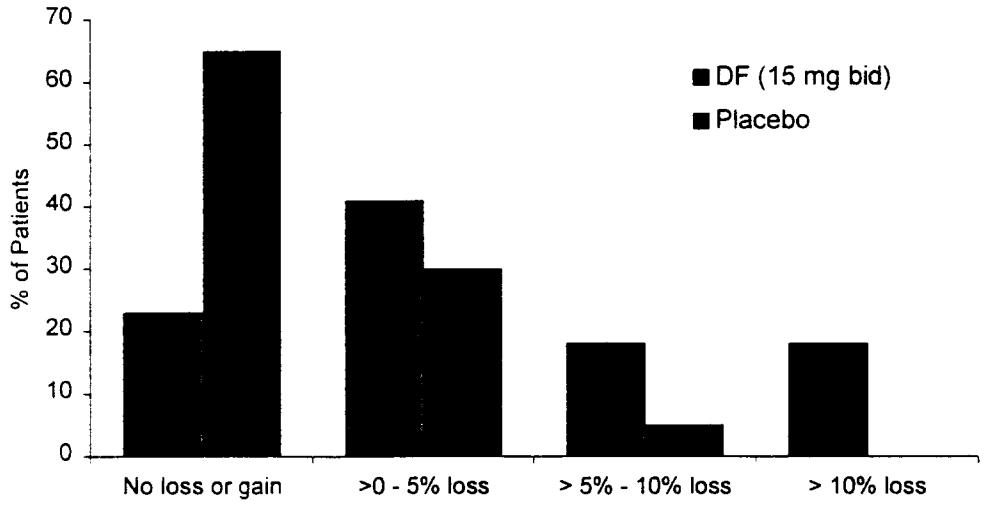
69 * p < 0.02 , ** p < 0.005 LOCF

Effect of Dexfenfluramine on % Weight Loss from Baseline Compared to Placebo - UK 18

% of Patients with Weight loss at Endpoint (6 mo)

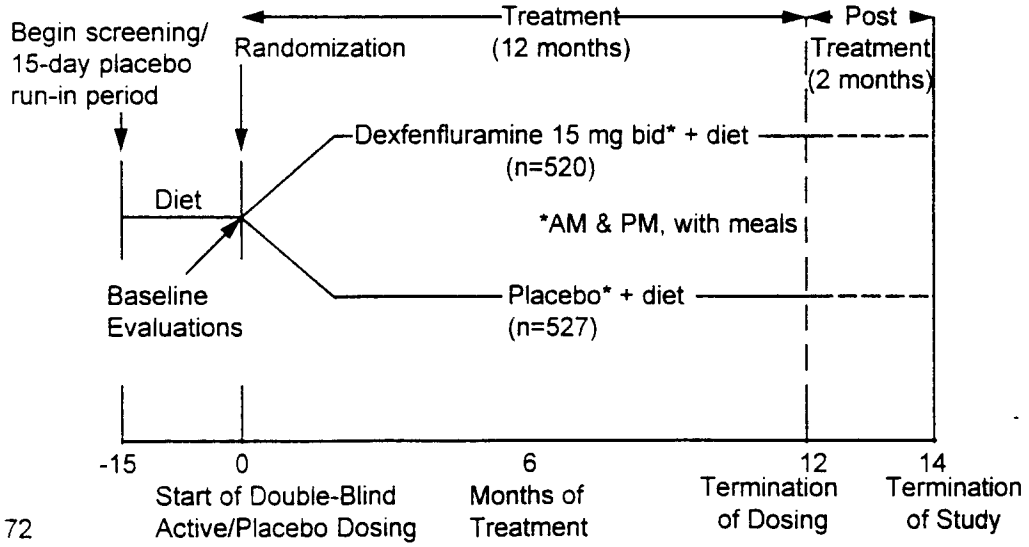
	≥ 5%			≥10%		
Analysis	DF	Placebo	p-Value	DF	Placebo	p-Value
LOCF	36%	5%	.013	18%	0%	.045
Completers	50%	6%	.006	25%	0%	.033

Effect of Dexfenfluramine on % Weight Loss from Baseline by Category Compared to Placebo - UK 18



71 $p \leq 0.014$ difference between groups LOCF

INDEX STUDY SCHEMA



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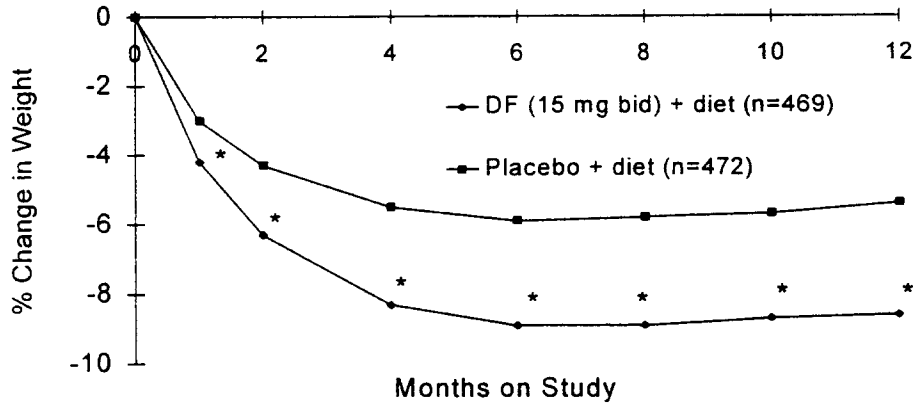
Demographic and Background Data - INDEX

Parameter	DF Mean (±sd)	Placebo Mean (±sd)
n	518	527
Males/Females	102/416	108/419
Age (yrs)	40.3 (±12.5)	41.6 (±12.5)
Height (cm)	164.4 (±8.9)	164.7 (±8.8)
Baseline Weight (kg)	96.5 (±19.6)	97.2 (±18.6)
Body Mass Index (kg/m^2)	35.6 (±5.9)	35.8 (±6.0)
Percent Ideal Weight MLIC	156.6% (±26.2)	157.6% (±26.3)

Prospective Protocol Defined Efficacy Endpoints - INDEX

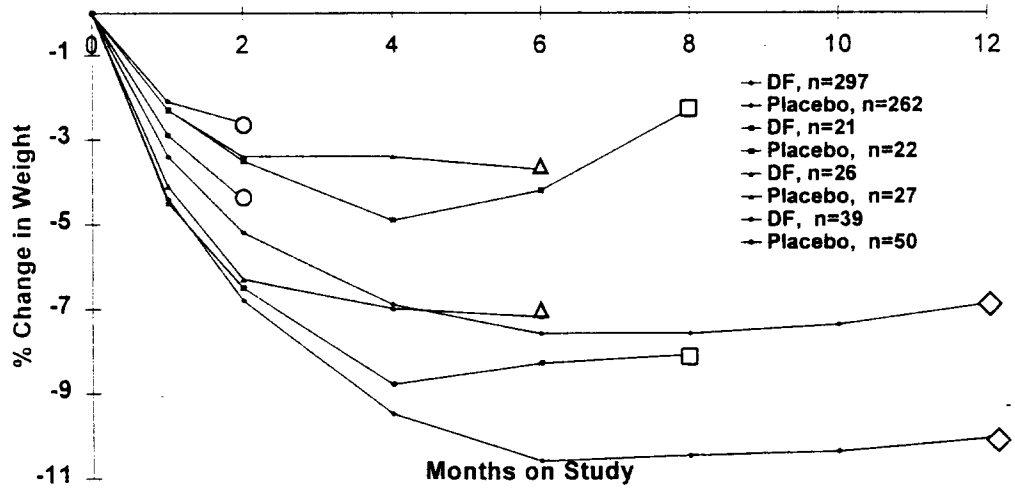
- Change from baseline in body weight
- % change in initial body weight
- % change in amount overweight
- % of patients losing 5, 10 and 15% of initial body weight

Effect of Dexfenfluramine vs. Placebo on Weight Loss over One Year- INDEX



75 *p<0.0001 LOCF

Effect of Dexfenfluramine vs. Placebo for Different Completer Groups - INDEX



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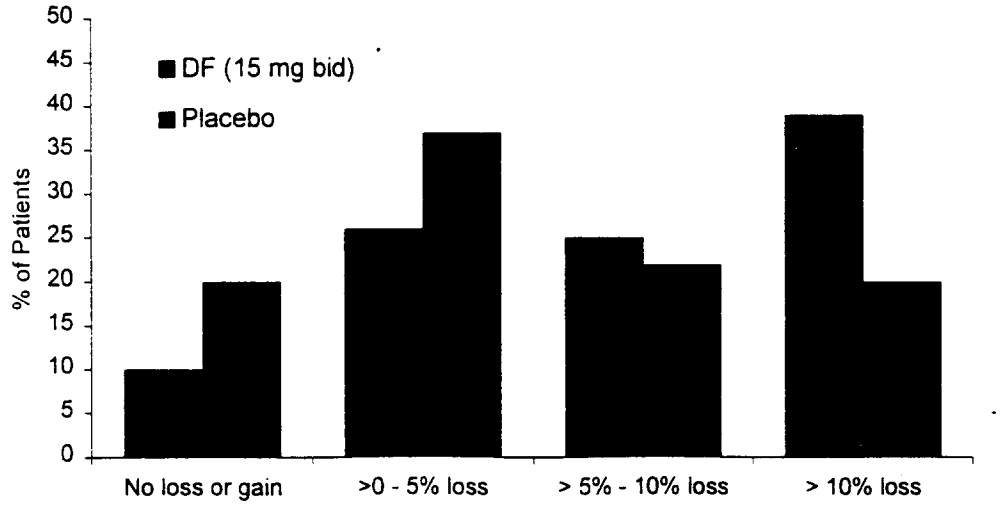
Effect of Dexfenfluramine on Weight Loss from Baseline Compared to Placebo - INDEX

% of Patients with Weight Loss at Endpoint (12 mo)

	≥ 5%			≥10%			≥15%		
Analysis	DF	Placebo	p-Value	DF	Placebo	p-Value	DF	Placebo	p-Value
LOCF	64%	43%	.0001	40%	21%	.0001	21%	10%	.0001
Completers	72%	50%	.0001	52%	30%	.0001	29%	16%	.001

Effect of Dexfenfluramine on % Weight Loss from Baseline by Category Compared to Placebo - INDEX



 p < 0.001 difference between groups

LOCF

Open Label, Long Term Trial

- Etude Francaise de l'Isomeride Multicentrique (EFIM)
  - 293 centers
  - One year treatment
  - n=1835 — 86% Female
  - Mean age — 41.6 ± 0.3 yrs
  - Mean weight at baseline — 84.6 ± 0.34 kg
  - Mean % of ideal body weight — 140.1 ± 0.49%
  - Mean BMI — 32 ± 0.11 kg/m^2

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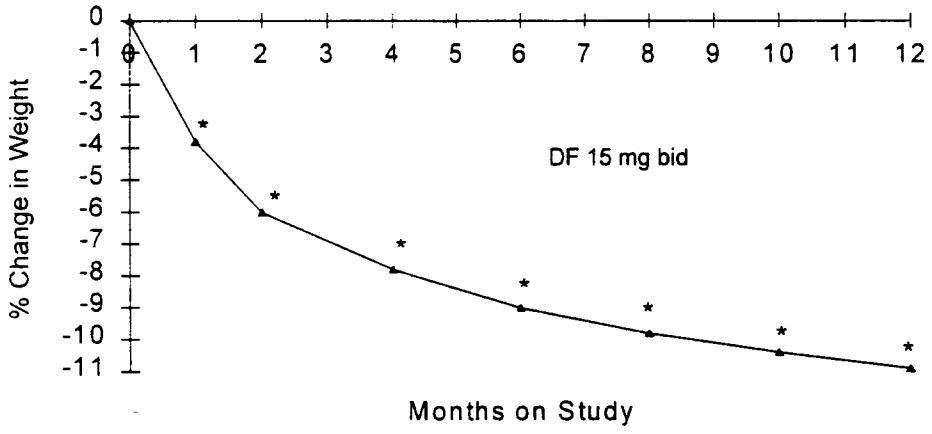
Effect of Dexfenfluramine on Weight Change - EFIM



80 * Significant differences were observed between each visit and from baseline

LOCF

Effect of Dexfenfluramine on % Weight Loss from Baseline by Category - EFIM

% of Patients with Weight Change at Endpoint (12 mo)

	No loss or gain	> 0 to 5% loss	> 5 to 10% loss	> 10% loss
DF	6%	18%	24%	52%

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LOCF

Patients with Co-morbid Conditions

- Obese hypertensive patients
- Obese diabetic patients
- Obese dyslipidemic patients

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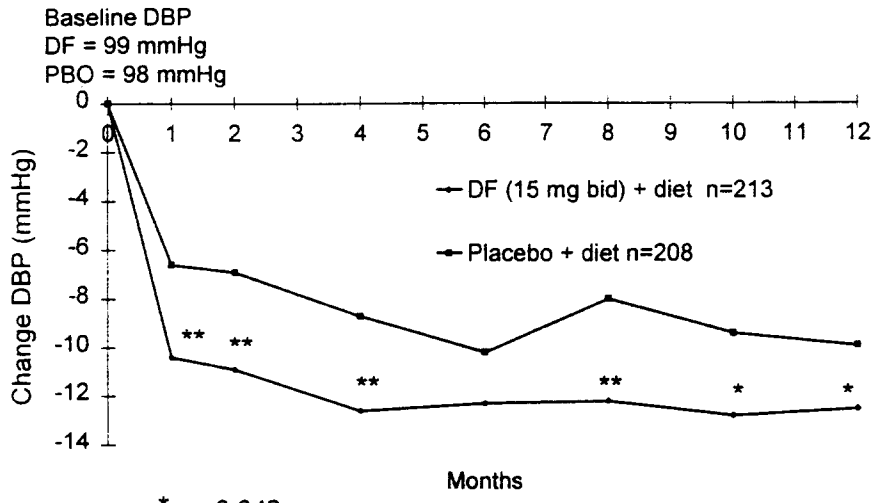
Change in Diastolic Blood Pressure in Hypertensive Patients - INDEX



*p ≤ 0.042
**p ≤ 0.001

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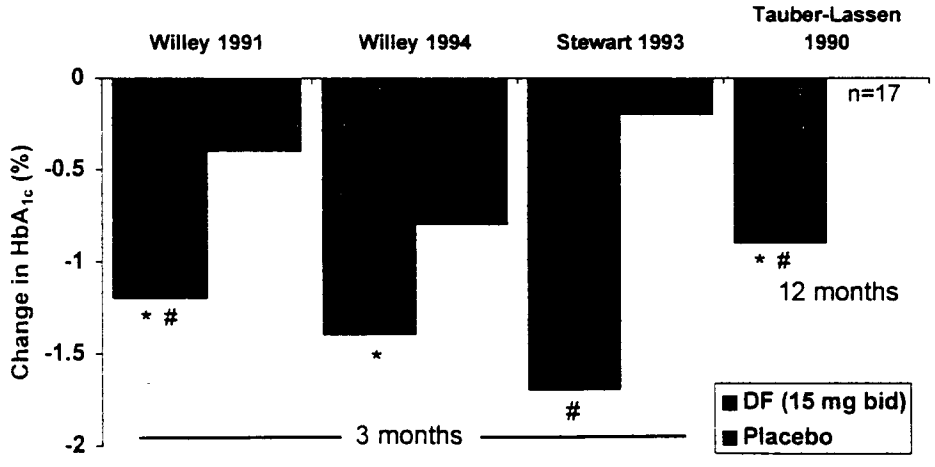
LOCF

Double-blind, Placebo-Controlled Studies of Dexfenfluramine In Obese Diabetic Patients



* p< 0.05 from baseline
# p< 0.05 from placebo

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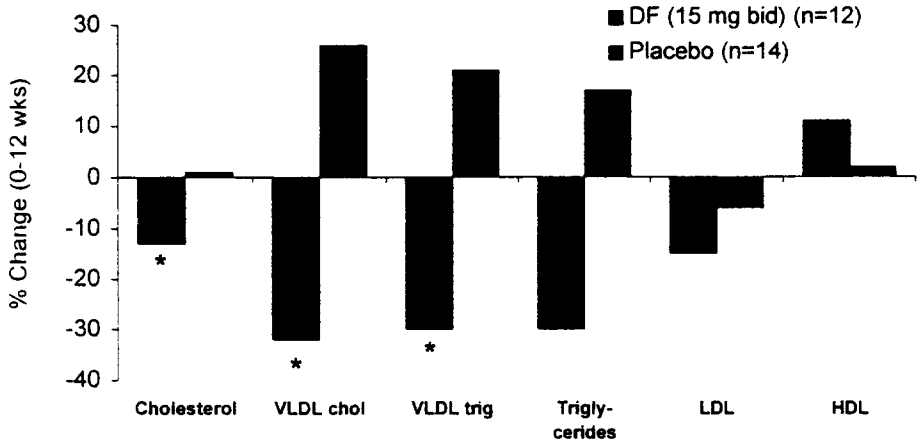
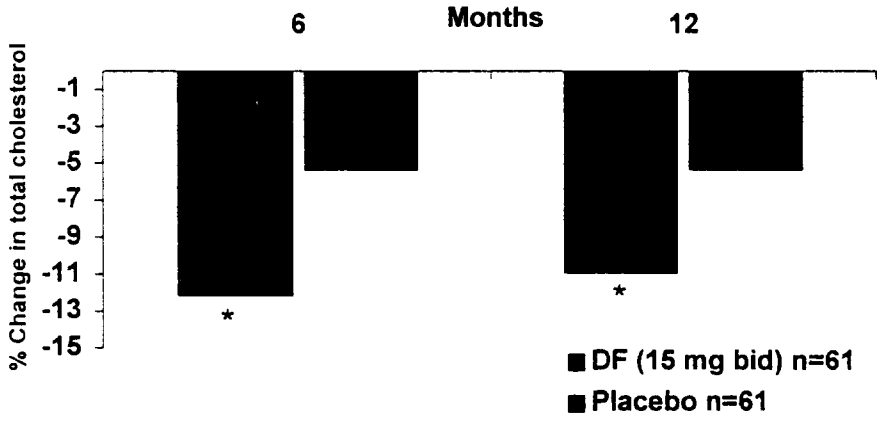
Effects of Dexfenfluramine on Lipids in Obese Dyslipidemics



* $p < 0.05$

Bremer et al., Int J Obesity, 1994

Effect of Dexfenfluramine on Total Cholesterol in Hypercholesterolemic Patients - INDEX



* $p \leq 0.002$

Conclusions: Efficacy

- In 18 of 19 placebo-controlled weight loss trials, dexfenfluramine produced statistically significantly superior weight loss compared to placebo
- Regardless of how weight loss is assessed, dexfenfluramine is significantly superior to placebo for the duration of treatment
- Subset analyses and special studies indicate that dexfenfluramine treatment favorably affects blood pressure, glucose control, and lipid profiles

Goal of Pharmacotherapy

- Limit drug exposure to those patients most likely to benefit
- Benefit in this analysis is a patient achieving a loss of $\geq$ 10% of their body weight by month 12

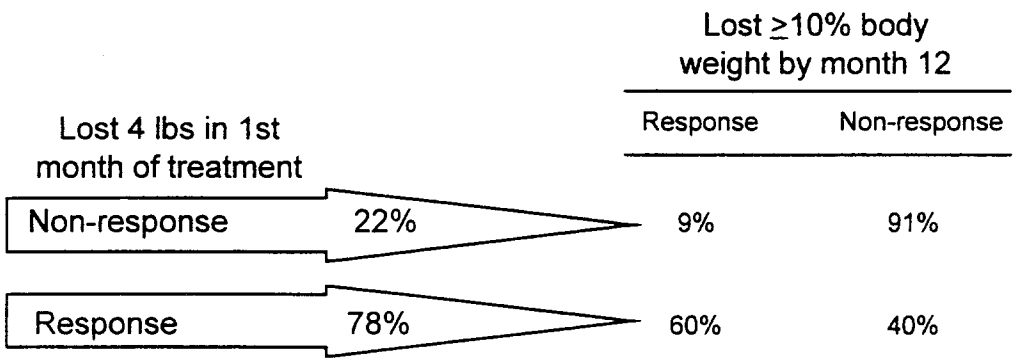
Response Predictors: Factors Analyzed

- Dexfenfluramine or placebo
- Gender
- Age
  - < 30 years
  - 30 to 50 years
  - ≥ 50 years
- Activity level
- Alcohol use
- Smoking status
- Duration of obesity
  - < 5 years
  - then 10 year increments
- Father obese
- Mother obese
- 4 lb weight loss in 1st month of treatment

Response Predictors of Patients Treated with Dexfenfluramine

- ≥ 4 lb weight loss in the 1st month of treatment (or 1 lb per week) predicts ≥ 10% body weight loss by 12 months

Response Predictors for Dexfenfluramine Treated Patients



INDEX

Conclusions: Response Predictors

- A 4 week trial of dexfenfluramine therapy is predictive of patients who are likely to achieve ≥ 10% weight loss with continuing treatment

Safety of Dexfenfluramine

- Scope of Safety Database
- Extent of Exposure
- Adverse Events
- Discontinuations
- Post - Marketing Experience

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NDA Obese Patient Database: Demographics

	DF	Placebo
n	3051	1138
Female (%)	84.5%	81.5%
Age Range (yrs)	41.3±12	40.8±12
Baseline Weight (kg)	87.9±17	94.3±18
Body Mass Index (kg/m^2)	32.8±5	34.6±6
% Ideal Body Weight	144.3±23	152.8±25

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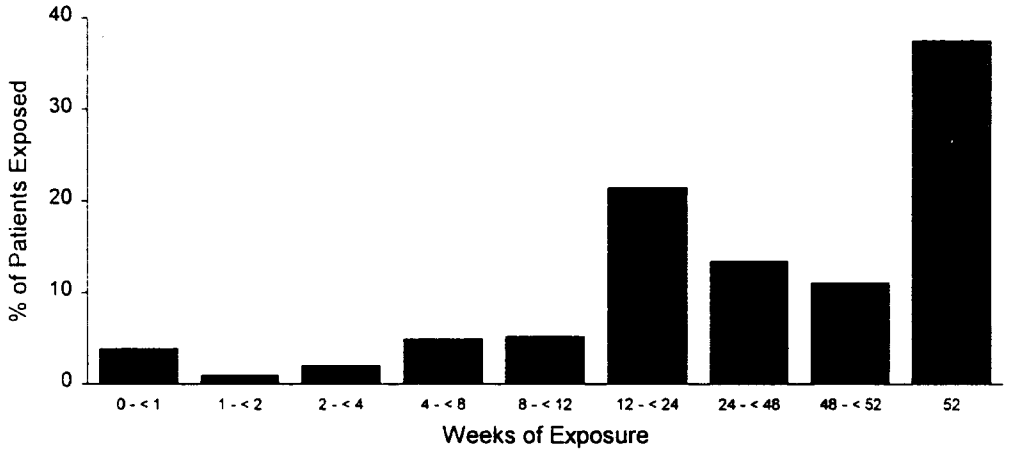
74 patients exposed to DF in more than one trial are counted only once

Duration of Exposure to Dexfenfluramine



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n = 3110

Statistically Significant Treatment-Emergent Adverse Events From Placebo-Controlled Trials (≥ 2%)

		% of DF 15 mg bid (n=1159)	% of Placebo (n=1138)
Body as a Whole:	Asthenia	15.8	10.7
	Chills	2.9	1.2
Gastrointestinal System:	Diarrhea	17.5	7.3
Metabolic/Nutritional System:	Thirst	2.8	1.1
Nervous System:	Dry Mouth	12.5	5.0
	Somnolence	7.1	3.4
	Vertigo	3.1	1.7
Respiratory System:	Bronchitis	3.4	1.8
Urogenital System:	Urinary Frequency	2.8	1.1
	Polyuria	2.1	1.0

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CNS Adverse Events Reported by ≥ 1% of the Patients

Preferred Term	DF (15 mg bid) (n=1159)	Placebo (n=1138)
Insomnia	19.9%	18.6%
Dry mouth	**12.5%**	**5.0%**
Somnolence	**7.1%**	**3.4%**
Nervousness	5.6%	5.7%
Dizziness	5.5%	4.0%
Depression	4.7%	3.6%
Vertigo	**3.1%**	**1.7%**
Emotional lability	3.1%	2.7%
Anxiety	2.8%	2.9%
Abnormal dreams	2.0%	1.4%
Thinking abnormal	2.0%	1.1%
Hypertonia	1.4%	1.3%
Libido increased	1.2%	0.9%
Paresthesia	1.1%	1.1%

Discontinuations: All Placebo-Controlled Studies

	DF 15 mg bid n (%)	Placebo n (%)
Total Patients	1159 (100.0%)	1138 (100.0%)
Completed Study	776 (67%)	712 (62.6%)
Discontinued:		
Adverse Event	80 (6.9%)	59 (5.2%)
Adverse Lab Experience	1 (0.1%)	4 (0.4%)
Ineffective Medication	58 (5.0%)	107 (9.4%)
Intercurrent Event	77 (6.6%)	71 (6.2%)
Lost to Follow-up	99 (8.5%)	94 (8.3%)
Non-Compliance	32 (2.8%)	44 (3.9%)
Patient Request	14 (1.2%)	28 (2.5%)
Other	21 (1.8%)	19 (1.7%)

Laboratory and Vital Signs

- Laboratory Effects: no clinically significant difference from placebo
  - 5 patients discontinued due to abnormal laboratory findings (1 DF, 4 Pbo)

- Vital Signs and Electrocardiograms: No adverse trends observed

Post-Marketing Surveillance & Experience

- Spontaneous reports received from prescribers of the marketed drug including anonymous reports from the National Adverse Drug Reactions (ADRs) Centers

- Serious or potentially serious adverse events and adverse event drop-outs observed during clinical investigations with dexfenfluramine

- Single experience reports in the scientific literature

Conclusions

- Dexfenfluramine, as an adjunct to diet, was found to produce significantly more weight loss than placebo for up to one year
- Significantly larger proportions of patients lose clinically significant amounts of weight when compared to placebo
- Well-tolerated, common adverse events are mild and self-limiting
- Post-marketing experience shows serious events are very rare

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IPPHS and Risk/Benefit of Pharmacologic Treatments

I. International Primary Pulmonary Hypertension Study (IPPHS)

II. Risk / Benefit

IPPHS - Origins

- Aminorex epidemic in early 60's
  - 400 to 1000 PPH cases in Switzerland, Austria, Germany
  - Rapid onset 6 months after marketing
  - Rate probably over 2000 per million (OR>1000)
- Cluster (10-15) cases of anorexigen associated cases in early 1990's
  - reported in *Brit Heart J*

International Primary Pulmonary Hypertension Study (IPPHS)

- Design and analysis
  - State-of-Art
  - Minimize bias
  - Analyze for bias and confounding
- Excellent Investigators
- Extraordinary Effort
- Limitations of Case-Control Design

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APPEARS THIS WAY
ON ORIGINAL

International Primary Pulmonary Hypertension Study (IPPHS)

- 95 cases - 21% exposed to anorexigens
- 355 controls - 6.5% exposed to anorexigens
- Anorexigen, obesity and systemic hypertension are independent risk factors for PPH with OR's of:

– Hypertension	=	2.5
– BMI > 30	=	2.4
– DF and F	=	3.8
– All anorexigens > 3mo	=	10.6

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International Primary Pulmonary Hypertension (IPPHS) Issues

- Diagnostic and Referral Bias
  - If referral were related to exposure, case exposure rates will be increased
  - There was considerable publicity (300 centers solicited, *Lancet* 1992, *Brit Heart J* 1993)
  - Undiagnosed cases likely to have less exposure (mistakenly diagnosed as COPD, CHD, etc.)

- Recall Bias (Despite Care Taken)
  - Cases may over report after multiple interviews with informed care providers
  - Controls may under report

International Primary Pulmonary Hypertension Study (IPPHS) Issues (Continued)

- Confounding by Indication
  - 32% of cases and 18% of controls were obese
  - If a condition is related to PPH, its treatment will be
  - Stratified and multivariate analyses were done for BMI<30 (OR = 2.9)

	Cases	Controls	Matched OR
Any anorexigen	20	23	4.4
BMI>30	11	7	5.0
BMI<30	9	16	2.9

Effect of Referral and Recall Bias --IPPHS--Example

- If 40% of cases (n=38) were not diagnosed and had the rate of exposure found for controls (6%), then their inclusion would drop the OR from 3.8 to 2.6
- Moreover, if only 8 of 355 controls had not recalled exposure the OR would further drop to 1.8 (95%CL 0.9-3.9)

THE POINT IS: RELATIVELY SMALL CHANGES DUE TO BIASES HAVE CONSIDERABLE IMPACT

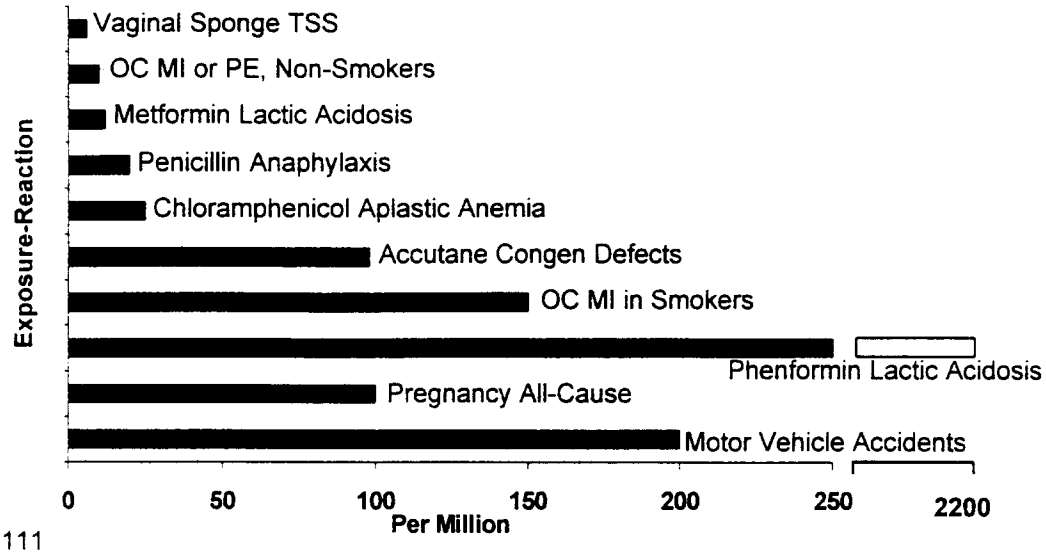
APPEARS THIS WAY
ON ORIGINAL

International Primary Pulmonary Hypertension (IPPHS) Study Relative and Absolute Risk

- DF/F odds ratio = 3.8
- All anorexigens for more than 3 months OR = 10.6
- Background PPH incidence 2 per million
- Maximum excess risk = (2 x OR) - 2 = 19.2 per million exposure

EVEN SEVERAL-FOLD MULTIPLES OF A RARE RISK RESULT IN RARITY

Drug Risks
Deaths Per Million (P-Y or P)



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International Primary Pulmonary Hypertension Study (IPPHS) - Conclusions

- The association with obesity and hypertension is important.
- Despite millions of exposures, only a handful of exposed cases have been found even after an intense search--there has been no epidemic.
- "The exact role of the anorexigens in the risk of PPH cannot, however be definitively established due to lack of knowledge of the pathogenic mechanisms, the lack of specificity of the effect within the class of anorexigens, the nonexclusion of all potential confounders and the low absolute risk."

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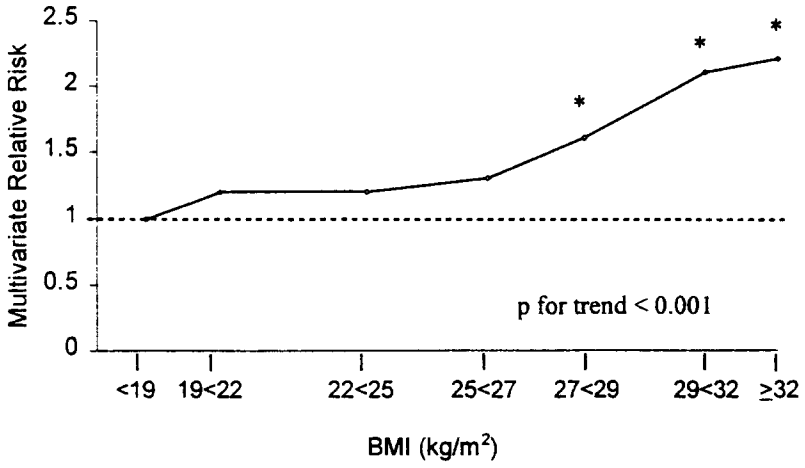
RISKS	BENEFITS
PPH 9.6 per million	Mortality change
(RR 10.6, Backgd rate 2 excess =2xRR-2) x 50% case-fatality rate	(Deaths avoided due to weight loss)

Nurses' Health Study

- 16 year follow-up of 115,000 nurses
- BMI and cause of death
- Age and smoking adjusted
- As BMI goes from 26 to 32:
  - All cause mortality increases 90% (968 excess lives lost per million per year)
  - CHD mortality increases 150% (575 excess lives lost per million per year)

BMI and All Cause Mortality Risk, Women

Never Smokers 1980-1992 (1168 deaths)



* $p < 0.05$

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Manson et al., NEJM, Sept 1995

Excess Deaths Per Million Patient Years*

BMI Change	Increased Risk (Delta)	Excess (Delta x 1076**)
27 to 32	2.2 - 1.4 = 0.80	860
28 to 32	2.2 - 1.6 = 0.60	645
29 to 32	2.2 - 1.8 = 0.40	430
30 to 32	2.2 - 2.1 = 0.10	110

*Derived from NHS-Manson-NEJM Sept. 14,1995. Female, non-smokers with stable weight. Multivariate RR's adjusted for age, physical activity, diet, alcohol, hormones.

**1076 - referent

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Benefit Model

Treat 1 million women with mean BMI of 32[a] with DF for 1 year
Achieving the following results persisting for a year

No. (%)[b]	Loss kg (% Body Wt)	Resultant BMI	Deaths Avoided[c]
200,000 (20%)	13.0 (15%)	27	172
200,000 (20%)	8.7 (10%)	29	86
200,000 (20%)	4.3 (5%)	30	22
Total Lives Saved Per Million Treated Per Year			280

[a]range 28-36, mean wt. 191 lb 5'5" or 87 kg and 1.65 m
[b]Conservative based on INDEX values (34% dropped BMI ≥5 units, 25% dropped 3 units, 30% dropped one unit)
[c]no. X delta from Manson tables

Benefit/Risk Ratios
DF Induced Weight Loss vs. PPH

Model	Deaths Avoided	Excess PPH Deaths*
INDEX study effectiveness	280	9.6
INDEX effectiveness limiting exposure to responders**	280	8.1

*Case-fatality equals 50%
**at 1 month-reduces exposure by 22% with little effect on benefit

Benefit/Risk Model

Conservative Estimate of Benefits Compared to Risks:

- Doesn't include morbidity and quality of life
- Conservative estimates of lives saved (nurses relatively young and healthy and effectiveness rate below that of INDEX)
- Reduce risk by continuing treatment in responders only
- Lives saved in future years aren't counted and risk probably will be limited to that found in the first year (depletion of susceptibles)

Can Weight Loss Reduce Mortality?

Weight Loss Results In:

1. Prompt improvements in glycemia, lipids, hypertension and quality of life.
2. 20% Reduction in all-cause mortality (vs. that found at BMI of 28)[1].
3. 50% Reduction in NIDDM with loss of 5 kg[2].
4. 69% "cured" of NIDDM and 43% "cured" of hypertension after GI surgery[3].

[1]ACS data AJE 1995

[2]Colditz et al. Ann Int Med 1995:481

[3]Swedish Obesity Study, 1995

Conclusion

1. IPPHS results may have been affected by publicity and referral patterns and recall bias.

2. Obesity is an independent risk for PPH.

3. Absolute risk of PPH, if present, is very small and below the risk of many commonly used medications.

4. Dexfenfluramine is effective and will prevent excess obesity-related deaths.

5. The benefit to risk ratio, particularly considering morbidity, is probably well over 50-fold.

Post-Approval Study Design Issues

- Size
- Duration
- Endpoints
- Control

WILL WORK WITH FDA

Post-Approval Studies -- Purposes

- Effectiveness in actual practice
- Compliance with labeling -- by both physician and patient
- Long term effects
- Safety assurance

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Obesity: A National Priority in the 1990s

- Chronic disease of increasing prevalence affecting 1 out 3 adult Americans
- A cause of serious morbidity and mortality: 300,000 deaths annually attributed to obesity
- Recognition of the genetic determinants of obesity has rendered obsolete the traditional view that obesity results simply from overeating and a sedentary lifestyle

Obesity: A National Priority in the 1990s

- Extensive clinical evidence that even moderate weight loss can reduce obesity-related morbidity and mortality
- Appreciation of the need for long-term use of effective appetite suppressants in patients who fail to lose or maintain weight loss by diet, exercise and behavior modification

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Dexfenfluramine: A New, Safe and Effective Therapeutic Agent

- Achieves long-term satiety by its effect on CNS serotonin
- Has been extensively tested clinically and found to be well tolerated
  - 19 double-blind, placebo-controlled trials involving > 4500 patients
  - Used by > 10 million patients over the 10 years the drug has been available
  - Marketed in 65 countries

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Dexfenfluramine: A New, Safe and Effective Therapeutic Agent

- There is compelling clinical evidence of dexfenfluramine's safety and ability to reduce and maintain body weight with favorable effects on co-morbidities
- Approval will add a significant treatment for obesity to the US physicians' armamentarium