

Breast Cancer

For a detailed statistical account of the breast cancer data see reviews by Drs. Pian and Stadel.

The original NDA submission contained 11 cases of breast cancer: one in placebo, one in orlistat 60mg, and nine in orlistat 120mg. All cases were limited to women 45 years of age and older and occurred in four of the seven randomized, double-blind trials. The table below lists relevant information about the cases.

ID #	Age	Race	Dose	Duration of Tx	Menopausal Status	ERT	Histology
52		Cauc	120mg	665 days	Post	Yes	Intraductal Lobular
46		Cauc	120mg	32 days	Pre	No	Infiltrating Ductal
61		Cauc	120mg	436 days	Post	No	?
54		Cauc	120mg	709 days	Post	Yes	Infiltrating Ductal
57		Cauc	120mg	173 days	Post	Yes	Lobular Carcinoma in Situ
51		Cauc	120mg	55 days	?	No	Infiltrating Lobular
54		Cauc	Placebo	443 days	Surg. Sterile	Yes	Intraductal
53		Cauc	120mg	191 days	Post	No	lobular
47		Cauc	60mg	36 days	Surg. Sterile	No	Ductal Invasive
55		Cauc	120mg	365 days	Surg. Sterile	No	Ductal
58		Cauc	120mg	344 days	Post	No	Ductal

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Conclusion

The mean percent reductions in body weight following one year of treatment with 120mg tid of orlistat and placebo were approximately 9.0% and 6.0%, respectively. This difference between drug and placebo falls short of the 5% difference recommended in the Division's Obesity Guidance Document. However, the efficacy of orlistat was evident in categorical analyses. For example, pooled data from five phase III studies indicate that nearly 60% of orlistat-treated patients and 31% of placebo-treated patients lost at least 5% of baseline body weight following one year of treatment ($p < 0.01$).

On balance, treatment with orlistat was associated with small, relative improvements in the levels of total and LDL cholesterol and systolic and diastolic blood pressure. In addition, there were modest improvements in the concentrations of fasting and post-load glucose and insulin following one year of drug treatment.

Collectively, the preclinical and clinical data indicate that orlistat reduces the absorption of vitamins D, E and β -carotene and leave open the question of its effect on vitamins A and K. Additional study of vitamin supplementation is needed to determine the most effective method to counteract the vitamin-depleting action of this drug.

The central issue surrounding the second orlistat NDA submission is the relationship between orlistat and breast cancer. When one takes into account the preclinical pharmacotoxicology data, it's reasonable to state that the excess cases of breast cancer in women randomized to orlistat vs. placebo is an unexpected finding that appears to lack biological plausibility, at least with respect to the drug acting as a tumor initiator. And while the findings may be due to chance, one cannot discount the possibility that orlistat has the potential to act as a breast cancer promotor, however unlikely this may also seem.

In the end, regardless of ones position on the plausibility that orlistat is causally related to an increased risk for breast cancer, we are left with some degree of uncertainty about the nature of this association. The ultimate question, I believe, is what level of uncertainty regarding a serious and common disease such as breast cancer is acceptable when considering the approvability of a modestly effective drug for the treatment of obesity?

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FEB 17 1998

MEMORANDUM

DATE: 17 February 1998

FROM: Bruce V. Stadel, MD, MPH /S/ [REDACTED]
Medical Officer/Epidemiology

TO: Solomon Sobel, MD
Director, Division of Metabolism
& Endocrine Drug Products

SUBJECT: Orlistat and Breast Cancer
NDA 20-766, Xenical (orlistat),
Hoffman-La Roche, Inc.

Attached is a nearly complete overview of information about orlistat and breast cancer from the phase 3 clinical trials; some data requested from Hoffman La-Roche are still pending submission.

Based on the breast cancer findings from the phase 3 clinical trials and the follow-up telephone survey of participants, I currently think there is a substantial preponderance of evidence that orlistat accelerates the development of breast cancer in women about 45 years of age or older when given orally at a dose of 120 milligrams three times per day.

Archive: NDA 20-776

HFD 510: Sobel

GTroendle

EColman

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HFD 715: ENevius

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ORLISTAT AND BREAST CANCER

1. BACKGROUND

1.1 BREAST CANCER

BREAST CANCER IS VERY RARE IN MEN AND IN WOMEN LESS THAN 20 YEARS OF AGE. FOR U.S. WOMEN WHO WERE 20 YEARS OF AGE OR OLDER WHEN RECEIVING A BREAST CANCER DIAGNOSIS IN 1997, THE RATE OF DIAGNOSIS FOR THE AGE GROUPS 20-44 YEARS AND 45 YEARS OR OLDER WERE APPROXIMATELY:

AGE GROUP 20-44: 25,500 CASES* IN 37,544,000 WOMEN,**
OR ABOUT ONE CASE IN EVERY 1472 WOMEN

AGE GROUP ≥45: 154,700 CASES* IN 49,020,000 WOMEN,**
OR ABOUT ONE CASE IN EVERY 319 WOMEN

*AMERICAN CANCER SOCIETY:

<http://www.cancer.org/statistics/97bcff/who.html>

**U.S. CENSUS BUREAU:

<http://www.census.gov/population/www/estimates/nation2.html>

1.2 ANTI-OBESITY DRUG USE

IN THE U.S. DURING 1997:

ABOUT [REDACTED] PRESCRIPTIONS FOR ANTI-OBESITY DRUGS WERE DISPENSED (estimated total for chain, independent, food store, and mail order pharmacies*), and

THE APPROXIMATE DISTRIBUTION OF ANTI-OBESITY DRUG PRESCRIBING BY SEX AND AGE WAS:

UNSPECIFIED [REDACTED]
MEN, ALL AGES [REDACTED]
WOMEN 20-44 YEARS OF AGE [REDACTED]
WOMEN ≥45 YEARS OF AGE [REDACTED]

(estimated from records of visits to office-based physician practices in the U.S.**)

[REDACTED]

2. DESCRIPTION OF THE ORLISTAT PHASE 3 CLINICAL TRIALS

THE PHASE 3 CLINICAL TRIALS OF ORLISTAT BEGAN IN 1992 AND ENDED IN 1996. THERE WERE SEVEN TRIALS IN TOTAL: FOUR IN THE U.S., TWO IN EUROPE, AND ONE IN THE U.K. ABOUT 80% OF THE PATIENTS STUDIED WERE CAUCASIAN WOMEN.

THE SEVEN PHASE 3 CLINICAL TRIALS WERE ALL RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED, PARALLEL-GROUP STUDIES, WHICH HAD LEAD-IN PERIODS DURING WHICH THE PATIENTS WERE TREATED WITH DIET AND PLACEBO. AT THE END OF THE LEAD-IN PERIODS, PATIENTS WERE RANDOMIZED TO TREATMENT WITH ORLISTAT OR PLACEBO. RANDOMIZATION WAS CARRIED OUT IN TWO STRATA, WHICH WERE DEFINED BY THE AMOUNT OF WEIGHT LOST DURING THE LEAD-IN PERIODS (≤ 2 kg versus > 2 kg for the six studies with 4-5 week lead-in periods, and $\leq 10\%$ versus $> 10\%$ of initial weight for the one study with a 6-month lead-in period).

THERE WERE THREE 1-YEAR TRIALS, TWO 2-YEAR TRIALS, AND TWO 2-YEAR CROSSOVER TRIALS WITH REASSIGNMENT OF STUDY DRUG AT THE END OF THE FIRST YEAR. A TOTAL OF 4188 PATIENTS WERE RANDOMIZED. OF THESE 4188 PATIENTS:

794 (19%) WERE MEN
1752 (42%) WERE WOMEN < 45 YEARS OF AGE AT RANDOMIZATION
1642 (39%) WERE WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION

3. BREAST CANCER IN THE ORLISTAT PHASE 3 CLINICAL TRIALS

3.1 BREAST CANCER DIAGNOSED "ON-STUDY" DURING THE CLINICAL TRIALS

DURING THE CLINICAL TRIALS, NO BREAST CANCER WAS DIAGNOSED IN MEN OR WOMEN < 45 YEARS OF AGE AT RANDOMIZATION.

ELEVEN CAUCASIAN WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION RECEIVED DIAGNOSES OF BREAST CANCER WHILE THEY WERE "ON-STUDY" DURING THE TRIALS. THE MEDIAN AGE AT DIAGNOSIS WAS 53 YEARS AND THE RANGE WAS 46-61 YEARS. FOUR OF THE ELEVEN CAME FROM THE RANDOMIZATION STRATUM THAT LOST ≤ 2 KG OR $\leq 10\%$ OF INITIAL WEIGHT DURING THE LEAD-IN PERIODS, AND SEVEN FROM THE STRATUM THAT LOST > 2 KG OR $> 10\%$ OF INITIAL WEIGHT. THE DISTRIBUTION BY TREATMENT GROUP AT THE BEGINNING OF THE TRIALS WAS:

9 CASES/747 WOMEN RANDOMIZED TO ORLISTAT 120 MG TID
1 CASE /225 WOMEN RANDOMIZED TO ORLISTAT 60 MG TID
0 CASE / 91 WOMEN RANDOMIZED TO ORLISTAT 30 MG TID
1 CASE /579 WOMEN RANDOMIZED TO PLACEBO

3.2.1 CASES IN WOMEN RANDOMIZED TO ORLISTAT 120 MG TID

OF THE NINE WOMEN WITH "ON-STUDY" DIAGNOSES OF BREAST CANCER AFTER RANDOMIZATION TO ORLISTAT 120 MG TID, EIGHT WERE DIAGNOSED WHILE TAKING ORLISTAT 120 MG TID OR WITHIN TWO WEEKS OF STOPPING, AND ONE WAS DIAGNOSED WHILE TAKING ORLISTAT 60 MG TID AFTER HAVING COMPLETED A YEAR OF ORLISTAT 120 MG TID, IN A CROSSOVER TRIAL.

BETWEEN RANDOMIZATION TO ORLISTAT 120 MG TID AND THE DIAGNOSIS OF BREAST CANCER IN THESE NINE WOMEN, THE TIME IN DAYS AND THE WEIGHT CHANGE, IN KILOGRAMS AND AS A PERCENT OF BASELINE, WERE AS FOLLOWS:

TIME (DAYS)	-----WEIGHT CHANGE-----	
	KILOGRAMS	PERCENT OF BASELINE
41	-3.5	
80	+1.4	
178	+2.9	
198	-10.7	
358	-12.6	
436	-3.8	
475	-2.6	
678	-6.4	
709	-0.1	
MEAN = 350	MEAN = -3.9	

THE PROCESS LEADING TO DIAGNOSIS OF BREAST CANCER BEGAN WITH ROUTINE MAMMOGRAPHIES FOR FIVE OF THE NINE WOMEN, WITH A ROUTINE PHYSICAL EXAMINATION FOR ONE, AND WITH BIOPSY OF SYMPTOMATIC BREAST MASSES FOR THREE.

THREE OF THE NINE WOMEN WERE TREATED WITH MASTECTOMY, TWO WITH BREAST SURGERY + RADIOTHERAPY, TWO WITH BREAST SURGERY + RADIOTHERAPY + CHEMOTHERAPY, AND ONE UNKNOWN METHODS. THE ONE WITH A DIAGNOSIS OF CARCINOMA IN SITU WAS TREATED WITH EXCISIONAL BIOPSY.

3.2.2 CASES IN WOMEN RANDOMIZED TO ORLISTAT 60 MG TID

THE ONE WOMAN WITH AN "ON-STUDY" DIAGNOSIS OF BREAST CANCER AFTER RANDOMIZATION TO ORLISTAT 60 MG TID WAS DIAGNOSED ONE DAY AFTER STOPPING ORLISTAT 60 MG TID, AND 37 DAYS AFTER RANDOMIZATION. SHE LOST 3.0 KG BETWEEN RANDOMIZATION AND DIAGNOSIS. THE PROCESS LEADING TO HER DIAGNOSIS BEGAN WITH AN EXAMINATION PRIOR TO ELECTIVE BREAST REDUCTION SURGERY. SHE WAS TREATED WITH MASTECTOMY.

3.2.3 CASES IN WOMEN RANDOMIZED TO PLACEBO

THE ONE WOMAN WITH AN "ON-STUDY" DIAGNOSIS OF BREAST CANCER AFTER RANDOMIZATION TO PLACEBO WAS DIAGNOSED WHILE TAKING PLACEBO, 443 DAYS AFTER RANDOMIZATION. SHE LOST 2.1 KG BETWEEN RANDOMIZATION AND DIAGNOSIS. THE PROCESS LEADING TO HER DIAGNOSIS BEGAN WITH ROUTINE MAMMOGRAPHY. SHE WAS TREATED WITH MASTECTOMY.

3.3 TELEPHONE SURVEY FOR BREAST CANCER DIAGNOSED "OFF STUDY" DURING THE CLINICAL TRIALS AND BREAST CANCER DIAGNOSED AFTER COMPLETION OF THE CLINICAL TRIALS

DURING JULY-OCTOBER 1997, 1454 (89%) OF THE 1642 WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION IN THE SEVEN PHASE 3 CLINICAL OF ORLISTAT WERE INTERVIEWED IN A TELEPHONE SURVEY. THIRTY OF THE 1642 WOMEN (2%) REFUSED TO BE INTERVIEWED, EIGHT (<1%) HAD DIED, AND 150 (9%) COULD NOT BE CONTACTED.

THE INTERVIEW RATE WAS 88% FOR WOMEN IN THE U.S. AND 89% FOR WOMEN IN EUROPE AND THE U.K. INTERVIEW RATES BY TREATMENT GROUP AT THE BEGINNING OF THE TRIALS WERE:

665/747 (89%) RANDOMIZED TO ORLISTAT 120 MG TID
280/316 (89%) RANDOMIZED TO ORLISTAT 30-60 MG TID
509/579 (88%) RANDOMIZED TO PLACEBO

OF THE 1454 WOMEN WHO COMPLETED THE TELEPHONE INTERVIEWS, THREE REPORTED DIAGNOSES OF BREAST CANCER THAT OCCURRED "OFF-STUDY" DURING THE CLINICAL TRIALS OR THAT OCCURRED AFTER COMPLETION OF THE TRIALS:

ONE REPORTED A DIAGNOSIS OF BREAST CANCER, AT 59 YEARS OF AGE, THAT OCCURRED 292 DAYS AFTER RANDOMIZATION TO PLACEBO IN A TWO-YEAR TRIAL. SHE HAD STOPPED PLACEBO 112 DAYS AFTER RANDOMIZATION.

ONE REPORTED A DIAGNOSIS OF BREAST CANCER, AT 55 YEARS OF AGE, THAT OCCURRED 1462 DAYS (4.0 YEARS) AFTER RANDOMIZATION TO ORLISTAT 120 MG TID IN A 2-YEAR TRIAL. SHE HAD COMPLETED THE STUDY.

ONE REPORTED A DIAGNOSIS OF BREAST CANCER, AT 51 YEARS OF AGE, THAT OCCURRED 1520 DAYS (4.2 YEARS) AFTER RANDOMIZATION IN A 2-YEAR CROSSOVER TRIAL TO ORLISTAT 120 MG TID FOR YEAR 1, FOLLOWED BY ORLISTAT 60 MG TID, FOR YEAR 2. SHE HAD COMPLETED THE STUDY.

3.4 FOLLOW-UP TELEPHONE SURVEY FOR THE FREQUENCY OF KNOWN RISK FACTORS FOR BREAST CANCER AT RANDOMIZATION, AND FOR THE FREQUENCY OF MAMMOGRAPHY DURING THE CLINICAL TRIALS

A FOLLOW-UP TELEPHONE SURVEY WAS DONE TO OBTAIN INFORMATION ABOUT THE FREQUENCY OF KNOWN RISK FACTORS FOR BREAST CANCER AT RANDOMIZATION, AND THE FREQUENCY OF MAMMOGRAPHY DURING THE CLINICAL TRIALS, BY TREATMENT GROUP AT THE BEGINNING OF THE TRIALS. THE RESULTS ARE:

	-----ORLISTAT-----		
	120 MG TID	30-60 MG TID	PLACEBO
FREQUENCY OF KNOWN RISK FACTORS FOR BREAST CANCER, AT RANDOMIZATION			
	-----MEAN AGE IN YEARS-----		
MENARCHE	12.6	12.6	12.6
FIRST LIVE BIRTH	23.2	23.2	23.1
MENOPAUSE	46.8	47.6	47.6
	-----PERCENT POSITIVE-----		
FAMILY HISTORY OF BREAST CANCER			
MOTHER	7	8	5
SISTER	5	5	7
NULLIPARITY	9	8	9
HISTORY OF EVER HAVING A SPONTANEOUS ABORTION	29	27	32
HISTORY OF EVER HAVING A BREAST BIOPSY	18	16	16
HISTORY OF HORMONE REPLACEMENT THERAPY	56	61	62
FREQUENCY OF MAMMOGRAPHY, DURING THE CLINICAL TRIALS			

3.5 DESCRIPTION OF THE CLINICAL TRIALS

TABLE 1 DESCRIBES THE SEVEN PHASE 3 CLINICAL TRIALS BY PROTOCOL NUMBER, GEOGRAPHIC LOCATION, YEAR BEGUN AND YEAR ENDED, NUMBER OF WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION, NUMBER OF WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION WHO COMPLETED THE TRIAL, AND THE NUMBER OF WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION WHO RECEIVED DIAGNOSES OF BREAST CANCER. TABLE 2 AND FIGURE 1 GIVE TIME-TO-WEIGHT LOSS DATA FOR PATIENTS TAKING ORLISTAT AND PATIENTS TAKING PLACEBO, IN THE FOUR CLINICAL TRIALS DURING WHICH BREAST CANCER WAS DIAGNOSED IN WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION TO ORLISTAT 120 MG TID (STUDIES NM14302, NM14185, BM14149, AND NM14161).

3.6 CASE REPORTS FOR THE WOMEN WITH BREAST CANCER DIAGNOSES

APPENDIX 1 GIVES CASE REPORTS FOR THE 11 WOMEN ≥ 45 YEARS OF AGE AT RANDOMIZATION WHO RECEIVED DIAGNOSES OF BREAST CANCER WHILE THEY WERE "ON-STUDY" IN THE CLINICAL TRIALS, AND FOR THE THREE WOMEN WHO REPLIED IN THE TELEPHONE SURVEY THAT THEY RECEIVED DIAGNOSES OF BREAST CANCER WHILE "OFF-STUDY" DURING THE TRIALS (N=1) OR AFTER COMPLETION OF THE TRIALS (N=2).

4. ATTACHMENT 1: STATISTICAL REVIEW BY DR. LEE PIAN, DATED 17 FEBRUARY 1998.

THERE ARE MINOR DIFFERENCES BETWEEN THE REVIEW BY DR. PIAN AND THE TEXT IN SECTION 3 ABOVE REGARDING AGE AT DIAGNOSIS OF BREAST CANCER AND THE NUMBER OF DAYS BETWEEN RANDOMIZATION AND DIAGNOSIS. THESE REFLECT MINOR VARIATIONS IN THE REPORTING OF DATA IN DIFFERENT PARTS OF THE NDA.

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TABLE 1

PHASE 3 CLINICAL TRIALS OF ORLISTAT
 -- WOMEN ≥45 YEARS OF AGE AT RANDOMIZATION --

PROTOCOL/ TREATMENT	RANDOMIZED N	COMPLETED N (%)	BREAST CANCER DIAGNOSIS N/ PATIENT ID NUMBERS
-----ONE YEAR STUDIES-----			
14119B			
UK, 1992-94			
120 MG TID	37	26 (70)	0
PLACEBO	38	24 (63)	0
14302			
USA, 1993-96			
120 MG TID	93	70 (75)	2/ [REDACTED]
60 MG TID	68	55 (81)	0
30 MG TID	91	74 (81)	0
PLACEBO	90	68 (76)	0
14336			
USA, 1993-96			
120 MG TID	73	63 (86)	0
PLACEBO	58	39 (67)	0
-----TWO YEAR STUDIES-----			
14149			
EUR, 1993-96			
120 MG TID	98	68 (69)	3 [REDACTED]
60 MG TID	95	64 (67)	1 [REDACTED]
PLACEBO	108	74 (69)	1 [REDACTED]
14161			
USA, 1993-95			
120 MG TID	66	45 (68)	1 [REDACTED]
60 MG TID	62	40 (65)	0
PLACEBO	57	29 (51)	0

TABLE 1 CONTINUED

-----CROSSOVER STUDIES-----

14119C
EUR, 1992-95

-----FIRST YEAR-----			
120 MG TID	153	131 (86)	0
PLACEBO	142	<u>115</u> (81)	0
		246	
-----SECOND YEAR-----			
120/120	60	54 (90)	1
120/PCB	68	57 (84)	0
PCB/120	51	43 (84)	0
PCB/PCB	<u>62</u>	53 (85)	0
	241		

14185
USA, 1992-95

-----FIRST YEAR-----			
120 MG TID	227	178 (78)	1
PLACEBO	86	<u>56</u> (65)	1
		234	
-----SECOND YEAR-----			
120/120	60	42 (70)	1
120/ 60	60	41 (68)	1
120/PCB	50	37 (74)	0
PCB/PCB	<u>56</u>	42 (75)	0
	226		

* DIAGNOSES REPORTED IN TELEPHONE SURVEY.

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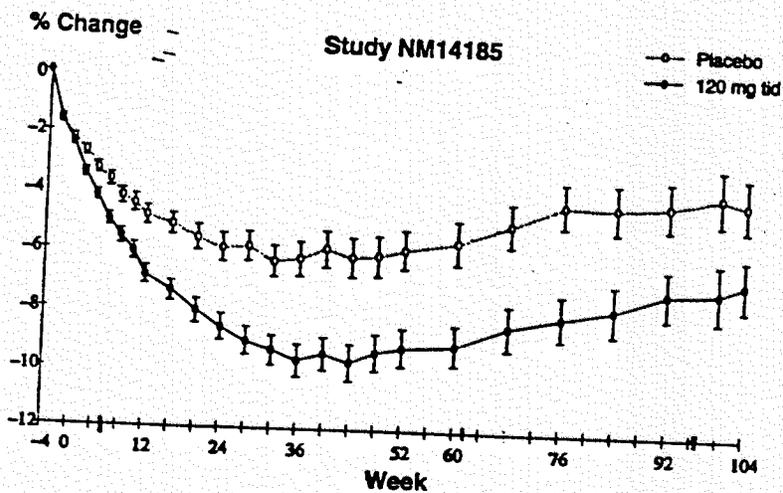
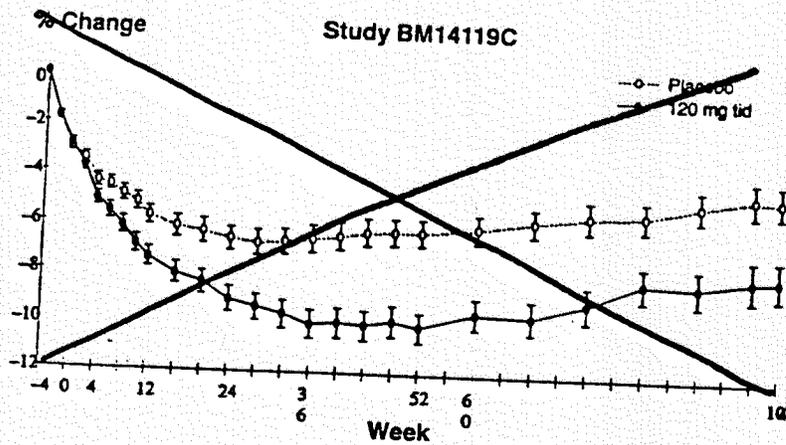
Table 19. Mean and Median Values at Scheduled Visits of Percent of Body Weight Regain from Start of Double-blind Treatment Intent-to-Treat Population NM14302

Treatment Group	Scheduled Visit	Value at Scheduled Visit				% Regain from Start of Double-Blind Treatment				
		N	Mean	SD	Median	N	Mean	SD	Median	
Placebo	Week -24	184	90.84	12.28	89.55					
	Day 1	184	80.51	11.66	79.50					
	Week 2	170	80.87	11.44	79.75	170	10.23	16.55	7.83	
	Week 4	155	80.73	11.54	80.10	155	10.29	16.96	7.95	
	Week 8	137	80.58	11.57	80.20	137	14.77	24.72	10.96	
	Week 12	144	81.06	11.50	81.10	144	17.03	27.97	16.46	
	Week 20	125	81.80	11.91	81.90	125	23.81	38.06	27.37	
	Week 28	119	82.97	12.78	83.50	119	35.07	45.93	35.77	
	Week 36	118	84.11	12.55	84.40	118	45.35	62.02	43.46	
	Week 44	106	84.20	13.60	83.85	106	51.39	54.19	52.09	
	Week 52	121	85.54	14.02	84.30	121	56.01	71.15	48.46	
	30 mg tid	Week -24	186	89.31	12.19	88.80				
		Day 1	186	79.25	11.58	79.40				
Week 2		167	79.96	12.23	79.90	167	8.47	15.76	5.77	
Week 4		171	79.25	11.86	78.10	171	8.20	16.66	5.74	
Week 8		139	78.93	11.69	77.50	139	9.31	20.44	7.69	
Week 12		156	79.24	11.88	77.65	156	13.31	24.98	10.06	
Week 20		147	79.74	12.01	78.20	147	18.04	33.86	14.81	
Week 28		130	81.07	11.93	79.85	130	29.53	40.79	30.39	
Week 36		116	80.99	12.69	79.35	116	35.74	46.21	37.06	
Week 44		113	82.93	12.85	81.20	113	46.07	50.13	52.83	
Week 52		119	82.92	13.46	81.80	119	53.27	53.80	52.11	
60 mg tid		Week -24	171	92.44	12.28	91.70				
		Day 1	171	82.44	11.66	81.70				
	Week 2	159	83.56	11.94	82.70	159	10.87	15.25	7.46	
	Week 4	155	82.58	11.72	81.30	155	8.89	15.52	6.90	
	Week 8	142	83.57	12.30	81.80	142	13.12	21.47	8.70	
	Week 12	143	82.63	12.07	80.50	143	13.07	23.68	9.41	
	Week 20	130	83.32	12.01	81.05	130	19.68	31.81	16.23	
	Week 28	108	83.17	12.34	80.80	108	27.36	41.30	22.90	
	Week 36	101	84.44	12.38	82.50	101	33.02	42.45	34.09	
	Week 44	88	84.73	12.81	82.75	88	37.56	47.93	32.58	
	Week 52	116	86.10	12.42	84.85	116	47.22	44.17	47.01	
	120 mg tid	Week -24	179	89.72	11.38	89.40				
		Day 1	179	79.86	11.14	78.70				
Week 2		169	80.19	11.56	79.10	169	6.49	13.23	4.95	
Week 4		157	80.05	11.08	79.20	157	3.33	14.54	3.48	
Week 8		130	79.89	10.94	79.50	130	3.65	17.19	1.46	
Week 12		144	79.53	11.68	79.00	144	2.08	25.60	0.00	
Week 20		127	79.80	12.17	78.50	127	7.65	33.03	7.46	
Week 28		109	81.06	12.02	81.40	109	14.25	38.16	13.07	
Week 36		100	82.15	12.66	82.60	100	21.30	42.96	20.14	
Week 44		99	82.00	11.86	81.80	99	26.82	42.45	27.40	
Week 52		113	82.17	11.65	82.00	113	32.36	47.84	36.11	

Least squares mean percent difference in body weight from placebo was statistically significant for the 120 mg treatment group (p<0.001), but not for the 30 mg or 60 mg treatment groups (Table 19).



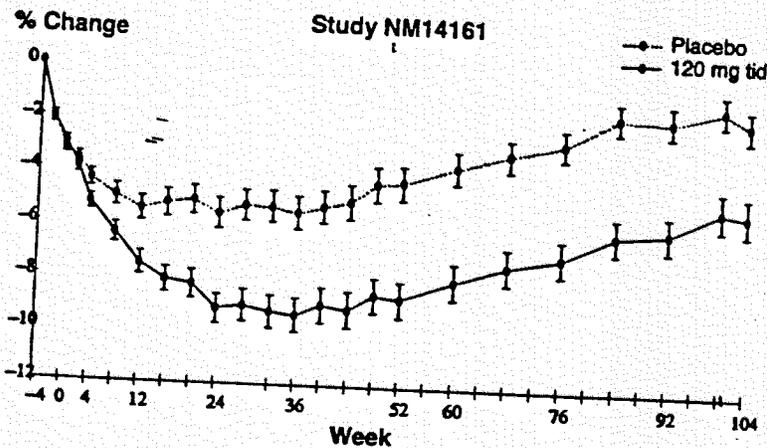
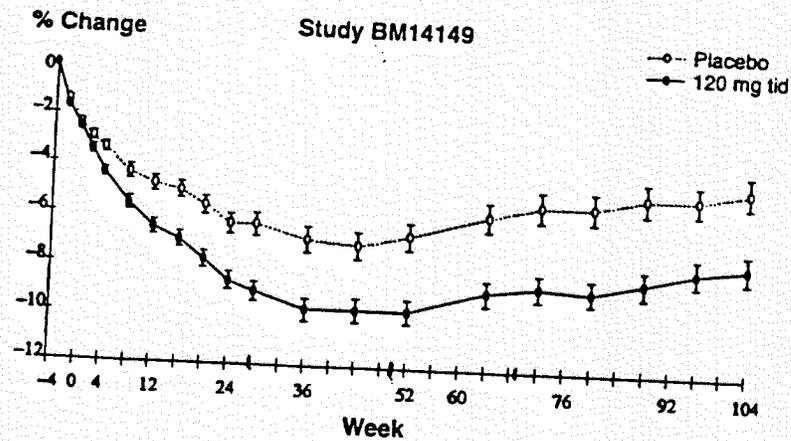
Figure 14 Mean Percent Change (\pm SEM) from Initial Body During 104 Weeks of Treatment
Studies BM 14119C, NM14185, BM14149, NM14161



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Figure 14 (cont.) Mean Percent Change (\pm SEM) from Initial Body
During 104 Weeks of Treatment
Studies BM 14119C, NM14185, BM14149, NM14161



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APPENDIX 1