

CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 020766

STATISTICAL REVIEW(S)

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG 22 1997

FROM: Mathematical Statistician (HFD-715)

THRU: *for* Edward Nevius, Ph.D.
Director, Division of Biometrics II. (HFD-715)

/S/ [Redacted]

8/22/97

SUBJECT: Incidence of Breast Cancer
Submission dated August 21, 1997

TO: File (NDA 20-766)

In the submission, the sponsor performed epidemiologic analyses on the breast cancer outcome during the trial and the trial plus survey periods. In the epidemiologic analyses, the incidence rates are expressed in person-years of follow-up for women 45 years or older instead of in the number of women 45 years or older. As expected in a memorandum dated August 20, 1997, the sponsor's results are consistent with our findings. Because in randomized clinical trials all subjects are followed for a constant period of time the results of the analyses based on person as the observation unit are similar (in the presence of a comparable dropout rate) to that when the person-time is the observation unit. The following table displays Fisher binomial confidence intervals of both 95% and 90% (appropriate for safety issue) for the orlistat incidence rates in comparison to placebo.

Relative Risk of Breast Cancer During Clinical Trial Plus Survey Periods
Women 45 Years or Older

Treatment	# of Patients	Person-Years of Follow-up	# of Cases	Relative Risk Versus Placebo (95% C.I.) (90% C.I.)	2-sided p-value
Placebo	579	1687	2	1	
30/60 mg	316	887	1	0.95 (0.02, 18.26) (0.033, 12.15)	1.0
120 mg	747	2306	11	4.02 (0.88, 37.35) (1.05, 25.35)	0.05 Mantel-Haenszel 0.08 Fisher 2 x 1-sided
Total	1642	4880	14		

/S/ [Redacted]

Lee-Ping Pian, Ph.D.
Mathematical Statistician

/S/ [Redacted]

Concur: Mr. Marticello

cc:

Arch NDA 20-766

HFD-510

HFD-510/EColman, BStadel, GTroendle, SSobel, MHess

HFD-715/LPian, Division 2 file, DMarticello

HFD-720/YTsong

Chron.

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: AUG 20 1997

FROM: Mathematical Statistician (HFD-715)

THRU: Edward Nevius, Ph.D. /S/ [REDACTED] 8-20-97
Director, Division of Biometrics II. (HFD-715)

SUBJECT: Incidence of Breast Cancer

TO: File (NDA 20-766)

In a teleconference dated August 19, 1997 the sponsor indicated that the survey report which will be submitted on August 21, 1997 uses the observed cases per person-years at risk for all randomized patients instead of number of women 45 years or older at randomization for the denominator. In a Memorandum dated May 23, 1997 which used the safety population for the denominator, the odds ratios of orlistat (30/60/120 mg) to placebo was 4.86 and the 95% confidence interval using the Exact method was (0.67, 213.2). The Fisher's Exact Test had a two-sided p-value of 0.1713. This reviewer expects that the sponsor's analysis utilizing the person-years at risk will be in the same ballpark if it utilizes the entire patient population as opposed to women 45 years or older.

Additional analyses on updated cases (8/13/97) with study as a stratification factor were performed. The results are displayed in Table 1 for both odds ratio and relative risk. The relative risk results are from Dr. Yi Tsong in Division of Biometrics III. It should be noted that results are similar for stratified and pooled analyses as well as for the various methodologies displayed in Table 1. Also, the odds ratios and relative risks are similar for the stratified analysis.

APPEARS THIS WAY ON ORIGINAL

Table 1. Analysis Stratified by Studies on Breast Cancer Incidence Updated on 8/13/97
Women 45 Years or Older

Study	120 mg Orlistat	Placebo	Analysis Results
			Stratified Analysis
NM14185	4/227	1/86	Odds Ratio (C.I.) 4.175 (0.877, 39.66) Exact p=0.082 (2 x one-sided) (1.005, 28.34) Mid-p corrected
BM14149	3/98	1/108	
NM14302	2/93	0/90	3.896 Mantel-Haenszel p=0.048 (M-H variance) (0.8686, 17.48) p=0.076 RGB variance
BM14119C	1/153	0/142	
NM14161	1/66	0/57	Relative Risk (C.I.) 4.127 (0.873, 39.051) Exact p=0.084 (2 x one-sided) 3.830 (0.898, 18.970) M-H, Breslow C.I. p=0.0494
NM14336	0/73	0/58	
BM14119B	0/37	0/38	
			Pooled Analysis
Total	11/747	2/579	Odds Ratio: 4.312 (0.935, 40.15) Exact p=0.048 (2-sided) p=0.065 (2 x one-sided) 4.312 (0.952, 19.53) M-H p=0.058 Chi-Square p=0.039

/s/

Lee-Ping Piat, Ph.D.
Mathematical Statistician

/s/

Concur: Mr. Marticello

cc:

Arch NDA 20-766

HFD-510

HFD-510/EColman, BStadel, GTroendle, SSobel, MHess ✓

HFD-715/LPian, Division 2 file, DMarticello

HFD-720/YTsong

Chron.

APPEARS THIS WAY ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
 PUBLIC HEALTH SERVICE
 FOOD AND DRUG ADMINISTRATION
 CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: AUG 15 1997
FROM: Mathematical Statistician (HFD-715)
THRU: Edward Nevius, Ph.D. [redacted] 8-15-97
 Director, Division of Biometrics II. (HFD-715)

SUBJECT: Incidence of Breast Cancer Updated on August 13, 1997

TO: File (NDA 20-766)

This is to update the recent findings of one new case in the placebo group and 2 new cases in the orlistat group of breast cancer from the preliminary retrospective follow-up report (Fax from Hoffmann-La Roche dated 8/14/97). Out of the 1642 women age 45 years or older at randomization, 1154 (70%) questionnaires were completed. The response rate from Europe is 57% (382/671) and from U.S. it is higher at 79.5% (772/971). For the three treatment groups the response rates are 66% (382/579) for placebo, 74% (235/316) for the 30/60 mg orlistat group, and 72% (537/747) for the 120mg orlistat group.

The odds ratios and the p-values from Chi-square Test and Fisher's Exact Test comparing the orlistat and placebo and the trend test on breast cancer rates of placebo, combined groups of 30 mg and 60 mg of orlistat, and 120 mg orlistat are displayed in the following tables for the original NDA and updated cases:

Breast Cancer Incidence from NDA - Women 45 Years or Older

Treatment	# (percent) of Breast Cancer		Odds Ratio	p-value	
				Chi-Square	Fisher's Exact
Placebo	1/579	(0.17%)			
30 & 60 mg Orlistat	1/316	(0.32%)	1.84	0.66	1.0
120 mg Orlistat	9/747	(1.20%)	7.05	0.031	0.05
Total	11/1642	(0.67%)		Trend Test: p=0.025	

Breast Cancer Incidence Updated as of 8/13/97 - Women 45 Years or Older

Treatment	# (percent) of Breast Cancer		Odds Ratio	p-value	
				Chi-Square	Fisher's Exact
Placebo	2/579	(0.35%)			
30 & 60 mg Orlistat	1/316	(0.32%)	0.92	0.94	1.0
120 mg Orlistat	11/747	(1.47%)	4.31	0.039	0.048
Total	14/1642	(0.85%)		Trend Test: p=0.023	

[redacted]
 Lee-Ping Piao, Ph.D.
 Mathematical Statistician

Concur: Mr. Marticello [redacted]

MEMORANDUM

**DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH**

DATE: JUN 24 1997
FROM: Mathematical Statistician (HFD-715)
THRU: Edward Nevius, Ph.D. [redacted] 6-24-97
Director, Division of Biometrics II. (HFD-715)
SUBJECT: Incidence of Breast Cancer
TO: File (NDA 20-766)

The memorandum dated June 3, 1997 used Fisher's Exact test to compare breast cancer incidence in women who were 45 years or older at the time of randomization between orlistat and placebo. According to Mr. Mark Boldrin from the Biostatistics Department of Hoffmann-La Roche, the sponsor's Table 2C (Fax dated 5/23/97) was incorrect in the number of women randomized to the 60 mg tid treatment group in Protocol 14302. Instead of the correct sample size of 91 randomized women age ≥ 45 years, the table showed 68. Therefore, in Table 1 of the above mentioned memorandum the total number of the Orlistat group should be 1063 (instead of 1040).

Dr. Bruce Stadel suggested using the test of trend on the response rates of breast cancer in the three groups of placebo, the combined groups of 30 mg and 60 mg of orlistat, and 120 mg orlistat. The results of the trend test and the estimation of odds ratios are in the following table.

Trend Test on Breast Cancer Incidence - Women 45 Years or Older

Treatment	# (percent) of Breast Cancer	Odds Ratio (95% C.I.)		p-value trend test
		Asymptotic	Exact	
Placebo	1/579 (0.17%)			0.02
30 & 60 mg Orlistat	1/316 (0.32%)	1.84 (0.11, 29.4)	(0.02, 144.3)	
120 mg Orlistat	9/747 (1.20%)	7.05 (0.89, 55.8)	(0.97, 309.5)	

[redacted]
Lee-Ping Piao, Ph.D.
Mathematical Statistician

[redacted]

Concur: Mr. Marticello

cc:
Arch NDA 20-766
HFD-510

APPEARS THIS WAY ON ORIGINAL

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: JUN 3 1997

FROM: Mathematical Statistician (HFD-715)

THRU: Edward Nevius, Ph.D. [redacted] 6/3/97
Director, Division of Biometrics II. (HFD-715)

SUBJECT: Incidence of Breast Cancer

TO: File (NDA 20-766)

Dr. Bruce Stadel summarized those women who were 45 years or older at the time of randomization in the attached table for all Phase III studies. The odds ratio of breast cancer of all patients on orlistat (30mg, 60 mg & 120 mg) was compared to placebo. Women 45 years or older at the first baseline randomization to 120 mg orlistat and placebo were also compared since 120 mg orlistat is the indicated dose.

Table 1. Breast Cancer Incidence, All Orlistat vs. Placebo - Women 45 Years or Older

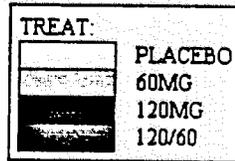
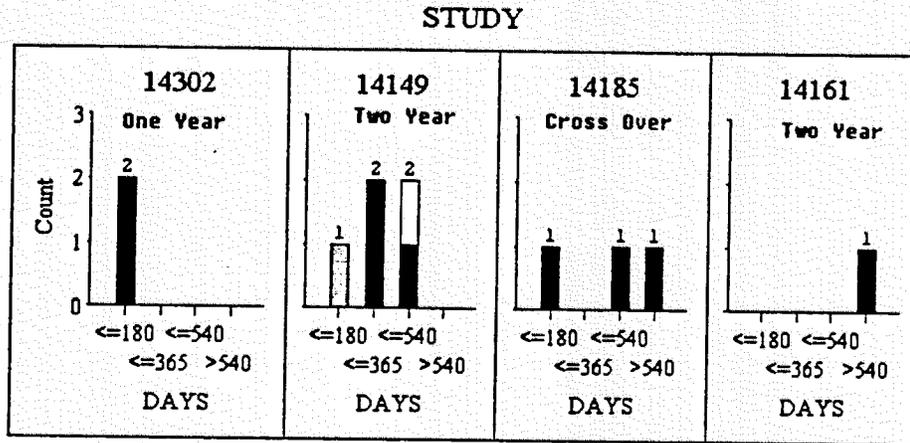
Treatment	# (percent) of Breast Cancer	Odds Ratio (95% C.I.)	p-value
Orlistat(30, 60, & 120 mg)	10/1040 (0.96%)	5.61 (0.79, 243.9) - Exact	0.108
Placebo	1/ 579 (0.17%)	(0.72, 43.9) - Asymp	0.100

Table 2. Breast Cancer Incidence, 120 mg Orlistat vs. Placebo - Women 45 Years or Older

Treatment	# (percent) of Breast Cancer	Odds Ratio (95% C.I.)	p-value
120 mg Orlistat	9/747 (1.20%)	7.05 (0.97, 309.5) - Exact	0.055
Placebo	1/ 579 (0.17%)	(0.89, 55.8) - Asymp	0.064

APPEARS THIS WAY ON ORIGINAL

The following figure displays the breast cancer cases over time for the four studies with breast cancer.



/S/ [Redacted]

Lee-Ping Pian, Ph.D.
Mathematical Statistician

Concur: Mr. Marticello

/S/ [Redacted]

cc:

- Arch NDA 20-766
- HFD-510
- HFD-510/EColman
- HFD-510/BStadel
- HFD-510/SSobel
- HFD-510/Gtroendle
- HFD-510/MHess
- HFD-715/LPian
- HFD-715/Division 2 file

APPEARS THIS WAY ON ORIGINAL [Redacted]

ORLISTAT AND BREAST CANCER

ALL NUMBERS REFER TO WOMEN 45+ YEARS OF AGE AT RANDOMIZATION BECAUSE THE YOUNGEST BREAST CANCER CASE WAS 47 YEARS OF AGE AT DIAGNOSIS.

PROTOCOL/ TREATMENT	RANDOMIZED N	COMPLETED N (%)	BREAST CANCER CASES N/DAYS OF TREATMENT
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-----ONE YEAR STUDIES-----

14119B			
120 MG TID	37	26 (70)	0
PLACEBO	38	24 (63)	0
14302			
120 MG TID	93	70 (75)	2/ 55,170
60 MG TID	68	55 (81)	0
30 MG TID	68	55 (81)	0
PLACEBO	90	68 (76)	0
14336			
120 MG TID	73	63 (86)	0
PLACEBO	58	39 (67)	0

-----TWO YEAR STUDIES-----

14149			
120 MG TID	98	68 (69)	3/ 191,344,379
60 MG TID	95	64 (67)	1/ 36
PLACEBO	108	74 (69)	1/ 443
14161			
120 MG TID	66	45 (68)	1/ 709
60 MG TID	62	40 (65)	0
PLACEBO	57	29 (51)	0

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

14119C

-----FIRST YEAR-----			
120 MG TID	153	131 (86)	0
PLACEBO	142	<u>115</u> (81)	0
		246	

-----SECOND YEAR-----			
120/120	60	54 (90)	0
120/PLBO	68	57 (84)	0
PLBO/120	51	43 (84)	0
PLBO/PLBO	<u>62</u>	53 (85)	0
	241		

14185

-----FIRST YEAR-----			
120 MG TID	227	178 (78)	1/ 32
PLACEBO	86	<u>56</u> (65)	0
		234	

-----SECOND YEAR-----			
120/120	60	42 (70)	1/ 665
120/60	60	41 (68)	1/ 436
120/PLBO	50	37 (74)	0
PLBO/PLBO	<u>56</u>	42 (75)	0
	226		

APPEARS THIS WAY ON ORIGINAL

M. Hess

MEMORANDUM

DEPARTMENT OF HEALTH AND HUMAN SERVICES
PUBLIC HEALTH SERVICE
FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

DATE: MAY 23 1997
FROM: Mathematical Statistician (HFD-715)
THRU: Edward Nevius, Ph.D. [redacted] 5-23-97
Director, Division of Biometrics II. (HFD-715)

SUBJECT: Incidence of Breast Cancer

TO: File (NDA 20-766)

The odds ratio of the breast cancer incidence were compared between orlistat and placebo. From the Xenical Advisory Committee Briefing Document p. 86, the placebo had 1466 patients and the orlistat had a total of 2722 patients with 186, 623, and 1913 patients treated with 30 mg, 60 mg and 120 mg, respectively. The cases of breast cancer were 1 in the placebo group and 9 in the orlistat group. Dr. Eric Colman requested a preliminary calculation of the odds ratio and its confidence interval. Table 1. displays the number and percentage of breast cancer incidence by treatment group and the confidence interval for the odds ratio using both the exact and the asymptotic method.

Table 1. Breast Cancer Incidence by Treatment Group - Safety Population

Treatment	# (percent) of Breast Cancer	Odds Ratio (95% C.I.)	p-value
Placebo	1/1466 (0.07%)	4.86 (0.67, 213.2) - Exact	0.1713
Orlistat	9/2722 (0.33%)	(0.62, 38.4) - Asymp	0.1338

When considering only the female patients, there were 1179 in the placebo group, and 2181 in the orlistat group (157, 30 mg, 485, 60 mg, and 1539, 120mg) in the safety population. The odds ratio and confidence interval were as follow:

Table 2. Breast Cancer Incidence by Treatment Group - Female Population

Treatment	# (percent) of Breast Cancer	Odds Ratio (95% C.I.)	p-value
Placebo	1/1179(0.08%)	4.88 (0.67, 214.1) - Exact	0.1695
Orlistat	9/21810.41%)	(0.62, 38.5) - Asymp	0.1328

The discreteness of the exact method makes the confidence intervals conservative. For instance, a nominal 95% confidence interval may have true confidence level 98%.

/S/

Lee-Ping Pien, Ph.D.
Mathematical Statistician

Concur: *jm* Mr. Marticello

/S/

5/23/97

cc:

Arch NDA 20-766

HFD-510

HFD-510/EColman

HFD-510/BStadel

HFD-510/SSobel

HFD-510/GTroendle

HFD-715/LPian

HFD-715/Division 2 file

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