ORIGINAL

Roche

ORIG AMENDMENT
BM

)ctober 30, 1998

ood and Drug Administration
ivision of Metabolism and Endocrine Drug Products, HFD-510
ffice of Drug Evaluation II
enter for Drug Evaluation and Research
TTN: DOCUMENT CONTROL ROOM 14B-19
500 Fishers Lane
ockville, Maryland 20857-1706

MTH 11/3/98

11/9/98

idies and Gentlemen:

e: **NDA 20-766 Xenical® (orlistat) Capsules, 120 mg**
Response to FDA Request of September 28, 1998 -
Identification of all Patients with a Breast Cancer Diagnosis

ference is made to the Agency's request included in a fax letter dated September 28, 1998. This letter ormed Roche of the Agency's intent to conduct an audit of the Phase 3b study sites and requested the ntification of all patients with a breast cancer diagnosis. The purpose of this submission is to provide rmation requested in the September 28 communication, see table below.

east Tumor Type	Protocol No./ Center No	Patient No.	Investigator/ Country	Treatment Group
ign Tumor	Protocol No. M37001 Center No. 007	78	Hughes United Kingdom	Xenical
ign Tumor	Protocol No. M37007 Center No. 0300	353	Irsigler Austria	Xenical
ast Cancer	Protocol No. M37020 Center No. 3016	263	Verhelst Belgium	Placebo
ast Cancer	Protocol No. M15421 Xendos Study	18010	Mathiesen Sweden	Placebo

se note that the one breast cancer occurred in the Xendos trial, which is not part of the Phase 3b gram, but is considered a Phase 3a study. Also, in the Xendos trial, pre-study mammograms are part he entry criteria for this study. There are no pre-study mammograms required for the Phase 3b ies.

BEST POSSIBLE

REVIEWS COMPLETED

12-7-98

DATE

Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199

Please feel free to contact the undersigned at the numbers provided if you have any questions regarding the information included in this submission.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ:LS/mb
Attachment
HLR No. 1998-2805

AMEND

Pharmaceutic

9.9.98 C 10.7.98 10.23.98

ATTACHMENT 3

ctober 13, 1998

and Drug Administration
ivision of Metabolism and Endocrine Drug Products, HFD-510
ffice of Drug Evaluation II
enter for Drug Evaluation and Research
TTN: DOCUMENT CONTROL ROOM 14B-19
500 Fishers Lane
ockville, Maryland 20857-1706

BEST POSSIBLE

adies and Gentlemen:

e: **NDA 20-766 Xenical® (orlistat) Capsules, 120 mg**
Response to FDA Request for Information: Phase 3b Vitamin Monitoring on Benign Tumor Information

eference is made to the Agency's fax dated September 3, 1998 requesting the sponsor's rationale for not onitoring fat-soluble vitamin levels in the US Phase 3b studies. Reference is also made to the Agency's equest for clarification on whether the two patients with benign breast tumors (see submission to NDA 20-766 dated September 9, 1998) continued treatment with Xenical.

The purpose of this submission is to provide the requested information which is found on the following pages. Please feel free to contact the undersigned regarding the information included in this submission at the numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J Jack

/s/ 10/27/98

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ:LK/js
Attachment
HLR No. 1998-2642

REVIEWS COMPLETED
CSO ACTION: ☐ LETTER ☒ N.A.I. ☐ MEMO
CSO INITIALS 10/27/98 DATE

27 Oct 98

10/26/98

Hoffmann-La Roche Inc. 340 Kingsland Street Nutley, New Jersey 07110-1199

October 7, 1998

NEW CORRESP

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

BEST POSSIBLE

Ladies and Gentlemen:

Re: **NDA 20-766 Xenical® (orlistat) Capsules, 120 mg**
Revised Proposal for Aggregate Data Set to Address Breast Cancer Observation in Phase 3a Studies

Reference is made to the approvable letter for NDA 20-766 dated May 12, 1998 which states that final approval of this application is contingent on submission of additional data from an aggregate data set, that supports a conclusion orlistat does not increase the risk of breast cancer.

Reference is also made to the teleconference between the Division and Sponsor on July 22, 1998 during which the Agency clarified the size of the aggregate data set recommended to resolve the breast cancer issue. The Agency recommended that the aggregate data set include both a greater number of total patients than the Phase 3a NDA database and that the total years exposure should be within ±20% of the orlistat exposure in Phase 3a for females ≥45 years of age. Based on the July 22 discussion and subsequent discussions with Dr. J. Bilsted, we are herewith providing a revised proposal for the aggregate data set and its planned submission schedule to the Agency.

In December 1998, the aggregate data set will be adequate to replicate the Phase 3a NDA database and a January 1999 submission of these data is planned. It is expected that the breast cancer safety data from this aggregate will support a conclusion that orlistat does not increase the risk of breast cancer in women ≥45 years of age and, as per our previous agreements with the Agency, should result in the approval of this application with labeling similar to that of pravastatin with respect to the breast cancer observation.

We are most willing to discuss this revised proposal for the aggregate data set and the planned submission schedule with the Agency. Please feel free to contact the undersigned at the numbers provided if you have any questions regarding this submission.

Sincerely,

[redacted] 10/19/98

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

[redacted] 22 Oct 98

REVIEWS COMPLETED
CSO ACTION:
☐ LE... ☐ A.I. ☑ MEMO
[redacted] 10/27/98
CSO

[redacted] Ltd. 10/26/98

MJJ:TN
Attachments
HLR No. 1998-2591

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

ORIGINAL

Roche

NEW CORRESP

/S/

September 9, 1998

CENTER FOR DRUG
REC'D
SEP 10 1998
HFD-510

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

/S/

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Response to FDA's Request for Additional Information on Two Cases of Benign Breast Tumors

Reference is made to our submission dated July 17, 1998 to this NDA which included information requested by the Division prior to the teleconference between the Division and Sponsor scheduled for July 22, 1998. Reference is also made to the July 22 teleconference during which the Agency requested following up information such as the mammography and pathology reports for the two patients with benign breast tumors. The purpose of this submission is to provide the information as requested.

A brief summary of these cases and the documents provided in this submission for each patient follows.

Study M37001/United Kingdom: This 6-month study is followed by an open-label extension (M37003). The double-blind, randomized study is a comparison of the efficacy and safety of orlistat versus placebo in obese patients with mild to moderate hypercholesterolemia.

After 6-month double-blind treatment and one month of open label treatment, a left breast lump was detected in a 54-year old female patient receiving orlistat. (The code was broken after the lump was [illegible] later, an ultrasound scan of the left breast showed no abnormality and a mammogram was performed which showed no evidence of abnormalities in either breast. Also, on clinical examination no abnormalities were detected. The reports for these examinations are provided in Attachment 1. The patient had a medical history of breast cysts.

Study M37007/Austria: A 24-week study of the effect of orlistat in the treatment of non-diabetic patients under a moderate hypocaloric diet.

BEST POSSIBLE

One month after starting the above-mentioned study and during a routine examination, a breast lump was found in a 36-year old female patient being treated with orlistat. The patient was prematurely discontinued from the study and two months later the mass was surgically removed and found to be benign. Treatment was blinded until study completion. Translations of the pathology, mammography and ultrasound reports are provided in Attachment 2 followed by copies of the original reports in German, see Attachment 3.

/S/

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

Since the July 22, 1998 teleconference, two cases of breast cancer have now been reported in placebo treated patients. One patient was a 53 year old female participating in Study M37020, a randomized, double-blind study being conducted in Belgium and the other patient was a 52 year old female participating in the Xendos trial in Sweden. Additional information has been requested for both patients and will be provided in the near future.

Please contact the undersigned at the numbers provided if you have additional questions regarding this submission.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J. Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ:LK/mi
Attachments
HLR No. 1998-2291

Roche

August 11, 1998

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Roche's Phase IIIb Audit Proposal

Reference is made to the teleconference with the Division on July 22, 1998 at which it was agreed that Roche would submit a proposal for the auditing of the Phase IIIb studies being conducted in Europe. These studies are being utilized as part of the aggregate database cited in the Agency's approvable letter dated May 12, 1998 to address the breast cancer issue only. The purpose of this submission is to present Roche's auditing proposal.

Roche is prepared to share with the FDA any occurrence of significant audit findings. We trust that this approach will not only provide better assurance to FDA of the quality of the Phase IIIb trials, but will also avoid any concerns by investigators who were not advised of the possibility of an FDA inspection when signing the protocol and contractual agreement with Roche regarding these studies.

If you have any questions concerning this submission, please contact the undersigned at the numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ:LS/mi
Attachments
HLR No. 1998-2032

Roche's Phase IIIb Audit Proposal

According to the procedures of F. Hoffmann-La Roche, Ltd., Phase IIIb and IV studies are conducted in conformance with the ICH GCP guidelines or the relevant local regulations whichever afford greater protection to the patient. In contrast to studies in Phase IIIa or earlier phases, Phase IIIb investigators outside the US are not made aware of nor are they trained for the possibility of an FDA inspection. However, as part of the contractual agreement with the sponsor, they are required to accept audits by the Roche QA department.

Because the European Phase IIIb program has assumed pivotal status (limited to breast cancer safety data only), Roche developed an intensive audit program which will assess the level of compliance of internal and site staff with the relevant regulatory standards. In accordance with the procedures of Roche's QA department, key aspects of the trials have been identified, and these will be audited in detail.

- Handling of and accuracy in reporting safety information by the investigator and sponsor staff
- Accuracy in reporting and follow-up of any results of breast examinations (e.g. physical examinations, mammographys, etc.) by investigators
- Diligent capture of all occurrences of breast cancer

The centers to be audited were selected on the basis of the following considerations:

- Total number of patients treated for a minimum period of six months
- Number of female patients equal to or above the age of 45 years
- Even representation of different study protocols and countries involved in the program

As a result of the above considerations, about 40 sites will be audited within the next 6 months, for details refer to Table 1.

TABLE I: XENICAL PHASE IIIB AUDIT PLAN

Protocol	Country	Total centers per protocol	Total Females >45 yrs per protocol	Number of centers to be audited	Number (%) female patients >45 yrs at centers to be audited
M 37002	Germany	57	92	4	35 (38%)
M 37004	Sweden	33	197	4	44 (22%)
M 37007	Austria	8	[1]182	3	99 (54%)
M 37007[2]	Austria	8	74	3[2]	59 (80%)
M 37018	Australia	8	96	4	72 (75%)
M 37001	UK	12	66	3	32 (48%)
M 37003[2]	UK	12	51	3[2]	27 (53%)
M 37009	UK	63	124	6[3]	11 (9%)
M 37005	Spain	10	96	1	24 (25%)
m 37006	Spain	11	119	1	24 (20%)
M 37014	Mexico	1	36	1	36 (100%)
M 37015	Mexico	1	24	1	24 (100%)
M 37013	Brazil	5	45	2	28 (62%)
M 37013	Argentina	1[4]	28	1	28 (100%)
M 37012	Argentina	5	61	2[5]	32 (52%)
Total 14 Protocols	Total 8 countries			Total 39 centers	

[1] Seventy four of these 182 patients continued into the open extension phase study
[2] This is the open extension phase of M37007. Centers and patients audited are the same for both of these studies.
[3] Three of these centers are the same as for M 37001 and M 37003.
[4] This same center is involved in both studies M 37012 and M37013 and so it will be audited for the two protocols concurrently.
[5] Including the center performing protocol M 37013.

Roche

July 17, 1998

Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Additional Information Requested for July 22, 1998 Teleconference

Reference is made to the Agency's facsimile dated July 15, 1998 requesting addition information to be provided prior to our scheduled teleconference on July 22, 1998. The purpose of this submission is to respond to the questions included in the July 15, 1998 fax.

Response to Question 1.

The data reported in Table 1 of May 9, 1998 facsimile indicated that 851 women 45 years of age and older are currently participating in the Phase 3b studies being conducted in Europe. Due to randomization and blinding, we estimate that these 851 women will be equally distributed between the drug and placebo groups. The data in this table is limited to women participating in the Phase 3b as of May 8, 1998.

The Submission dated May 27, 1998 is the aggregate database proposal which includes the Phase 3b studies currently ongoing in Europe. For the Phase 3b studies in Europe we project that in December, 1998 we will have approximately 1,898 women, 45 years of age and older enrolled in these studies. Again, due to randomization etc, we anticipate equal distribution of this population in the drug and placebo groups, hence approximately 949 women in each group. This number is substantially higher than the number of women in the May 9 facsimile as enrollment is continuing in these studies, and the aggregate database is a projection of the number of women exposed to orlistat and placebo as of December 1998.

Response to Question No. 2.

The list of Phase 3b studies that have been completed and those that are still in progress with their estimated dates of completion (last visit for last patient) are presented in Attachment 1. This list of studies are the studies which comprise the Phase 3b studies from which estimates of women 45 years of age and greater were included in the aggregate database presented in the submission dated May 27, 1998.

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

The first two tables in Attachment are the completed and ongoing placebo-controlled trials in the European Phase 3b program. The last two tables are the completed and ongoing non-placebo controlled trials in the European Phase 3b program.

Response to Question No. 3

As of July 16, 1998, there were no cases of breast cancer reported in the Phase 3b studies; however, for two patients, masses in the breast were reported. Both events turned out to be not malignant. A brief discussion of these cases follows.

Study M37001: This 6-month study is followed by an open-label extention (M37003). The double-blind, randomized study is a comparison of the efficacy and safety of orlistat versus placebo in obese patients with mild to moderate hypercholesterolaemia.

After 6-month double-blind treatment and one month of open label treatment, a left breast lump was detected in a 54-year old female patient receiving orlistat. One month later, an ultrasound scan of the left breast showed no abnormality and a mammogram was performed which showed no evidence of abnormalities in either breast. Also, on clinical examination no abnormalities were detected. The patient had a medical history of breast cysts.

Study M37007: A 24-week study of the effect of orlistat in the treatment of non-diabetic patients under a moderate hypocaloric diet.

One month after starting the above-mentioned study and during a routine examination, a breast lump was found in a 36-year old female patient being treated with orlistat. The patient was prematurely discontinued from the study and two months later the mass was surgically removed and found to be benign.

Response to Question No. 4

The Patient Informed Consent forms for each study are provided as requested, see Attachment 2 for these documents for protocols M37046, M37047, M37048 and M37049 respectively.

Protocol M37046, the study in peri-and post-menopausal women, was reviewed and approved by the IRB pending revisions to the Patient Informed Consent form for this study. Both the original consent form and the revised consent form for Protocol M37046 are provided in this submission. The consent form for this study is still being discussed with the IRB and the revised form may not represent the final version of the form.

For Protocols M37047 (diabetics inadequately controlled with insulin), M37048 (diabetics inadequately controlled with Metformin) and M37049 (hypertensive patients inadequately controlled with antihypertensive medications), the IRBs had not met to discuss these studies.

We are also providing a copy of the Investigational Drug Brochure for these studies, see Attachment 3.

If you have any questions concerning this submission, please contact the undersigned at the numbers provided.

Sincerely,

HOFFMANN-LA ROCHE INC

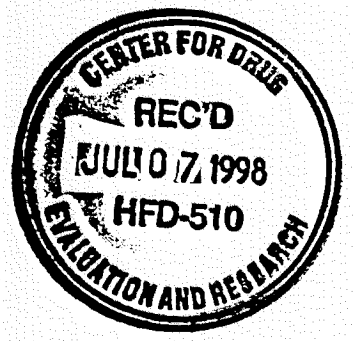
Margaret J. Jack

Margaret J. Jack
Program Director
(973) 235-4463 (telephone)
(973) 562-3700/3554 (fax)

MJJ:LS/bn
Attachments
HLR No. 1998-1817

Roche

July 6, 1998



Food and Drug Administration
Division of Metabolism and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120 mg
Additional Information Requested for Non-US Phase 3b Studies

Reference is made to the Agency's request included in a telefax dated May 20, 1998. Specifically, the durations of exposure of women, 45years and older, at the time of randomization in selected non-US Phase 3b studies (protocols M37007, M37002, M37004, M37001 and M37009) were requested in the telefax. The data requested is tabulated immediately following this letter.

Please contact the undersigned if you need additional information or clarification of this information.

Sincerely,

HOFFMANN-LA ROCHE INC

Margaret J Jack

Margaret J. Jack
Program Director
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MJJ:LS/mi
Attachment
HLR No. 1998-1703

Hoffmann-La Roche Inc. 340 Kingsland Street
Nutley, New Jersey 07110-1199

WOMEN EQUAL OR ABOVE 45 AT RANDOMIZATION IN MENTIONED PROTOCOLS

EXPOSURE	PROTOCOLS					TOTAL
	M37001	M37002	M37004	M37007	M37009	
Group 1 : On drug						
> 0 to < 3 months	0	27	1	0	74	102
>= 3 to < 6 months	0	18	7	0	53	78
>= 6 to < 9 months	0	9	61	0	0	70
>= 9 to < 12 months	0	13	30	0	0	43
12 months or more	0	12	79	0	0	91
Sub-Total	**0**	**79**	**178**	**0**	**127**	**384**
Group 2 : Off drug for less than 1 month						
> 0 to < 3 months	0	0	0	0	0	0
>= 3 to < 6 months	0	0	0	0	0	0
>= 6 to < 9 months	0	0	0	0	0	0
>= 9 to < 12 months	0	0	0	0	0	0
12 months or more	0	0	0	0	0	0
Sub-Total	**0**	**0**	**0**	**0**	**0**	**0**
Group 3 : Off drug for more than 1 month						
> 0 to < 3 months	8	2	10	8	3	31
>= 3 to < 6 months	47	5	2	63	0	117
>= 6 to < 9 months	10	0	3	20	0	33
>= 9 to < 12 months	0	10	0	0	0	10
12 months or more	0	0	0	0	0	0
Sub-Total	**65**	**17**	**15**	**91**	**3**	**191**
TOTAL	**65**	**96**	**193**	**91**	**130**	**575**

NOTE: These protocols are double blind trials and this table reflects randomized patients allocated either to Placebo or Orlistat treatment.

Roche

May 27, 1998

Food and Drug Administration
Division of Metabolic and Endocrine Drug Products, HFD-510
Office of Drug Evaluation II
Center for Drug Evaluation and Research
ATTN: DOCUMENT CONTROL ROOM 14B-19
5600 Fishers Lane
Rockville, Maryland 20857-1706

Ladies and Gentlemen:

Re: NDA 20-766 Xenical® (orlistat) Capsules, 120mg
Proposal for Aggregate Database Addressing Breast Cancer and
Request for Teleconference to Discuss Aggregate Database Proposal

Reference is made to the May 11, 1998 teleconference between the sponsor and the Division discussing various aspects of the Xenical NDA approval process and the aggregate database to be utilized to replicate the NDA database consisting of the four Phase 3a studies in which breast cancer was observed in some patients. This aggregate database will be utilized to support the conclusion that treatment with orlistat 120 mg does not increase the risk of breast cancer in females ≥45 years of age. The purpose of this submission is to provide the Agency with the proposal for the aggregate database previously described.

We are also herewith requesting a teleconference with the Division to discuss the proposed aggregate database and suggesting either the week of June 1 or June 8 as a possible time frame for this discussion.

Please contact the undersigned with possible time frames for the request teleconference or if you have any questions concerning this submission.

Sincerely,

HOFFMANN-LA ROCHE INC.

Margaret J Jack

Margaret J. Jack
Program Director
Drug Regulatory Affairs
(973) 235-4463 (Telephone)
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MJJ:LS/mi
Attachment
HLR No. 1998-1367

Proposal for Aggregate Database