Three placebo-treated and 18 orlistat-treated patients withdrew prematurely from the study because of adverse events (or laboratory abnormality) in various body systems. The number of patients withdrawing for adverse events for the placebo, 30 mg tid, 60 mg tid, 120 mg tid, and 240 mg tid groups was 3, 7, 6, 2 and 3 respectively. Eleven patients withdrew because of GI adverse events, 10 of whom were treated with orlistat.

There were 16 markedly abnormal laboratory values in both the placebo and orlistat 30 mg tid groups, 7 in the 60 mg tid group, 9 in the 120 mg tid group and 11 in the 240 mg tid group. The types and frequency of markedly abnormal laboratory values were similar among the placebo- and orlistat-treated groups. The most common markedly abnormal laboratory parameter, occult blood in the feces, occurred in 5% of placebo-treated patients, 7% of patients treated with orlistat 30 mg tid, 4% of patients treated with 60 mg tid and 2% of patients treated with 120 mg tid and 2% of patients treated with 240 mg tid.

Between 15% and 20% of patients in all treatment groups started the double-blind treatment period with an ECG abnormality. The most common abnormalities were sinus bradycardia, non-specific ST or T wave changes, left axis deviation and sinus arrhythmia. Between 5 and 8 patients per treatment group developed an ECG abnormality after having a normal baseline assessment. No obvious differences in ECG values could be discerned between placebo and the orlistat-treated groups. The most common ECG abnormalities emerging during treatment were similar to those abnormalities observed at baseline; these include sinus bradycardia, sinus arrhythmia, non-specific ST or T wave changes and left axis deviation.

The mean levels of vitamins A, D, and E and beta-carotene remained within the normal range throughout the study in all treatment groups. There was a statistically significant decrease in the levels of vitamin E and beta-carotene in the orlistat treatment groups (least squares mean) compared with the placebo treatment group after 24 weeks of treatment. The greatest difference between the orlistat and placebo treatment groups after 24 weeks of treatment was in the beta-carotene level. The mean percent decrease from the start of double-blind treatment in orlistat-treated patients was 15% to 36% (depending upon dose) compared with an increase in mean percent of 8% among placebo-treated patients. A statistically significant decrease in vitamin D was also noted only for the orlistat 240 mg tid group.

Gallbladder ultrasound scans were performed at both the start of double-blind treatment and after 24 weeks of treatment. The following proportions of patients had normal results at the start of treatment and abnormal results during follow-up in the placebo, 30 mg orlistat group, 60 mg orlistat group, 120 mg orlistat group and 240 mg orlistat groups, respectively: 3 of 72 (4.2%), 3 of 74 (4.1%), 6 of 75 (8.0%), 5 of 74 (6.8%), 6 of 71 (8.5%). Of the new abnormalities reported, one patient in the placebo and the orlistat 30 mg group had gallstones, while two patients in the orlistat 60 mg tid group had gallstones, three patients in the orlistat 120 mg tid group had gallstones and one patient in the orlistat 240 mg tid group had gallstones. Of all the patients in study who entered with an abnormal baseline gallbladder ultrasound, none developed a new case of stones. About one-quarter to one-third of patients entering with an abnormal baseline gallbladder ultrasound, had a normal follow-up gallbladder ultrasound.

PHARMACODYNAMIC RESULTS:

There were dose-dependent increases in mean fecal fat values after 24 weeks of treatment with orlistat: 11.5 g/day, 15.4 g/day, 18.5 g/day, and 23.5 g/day in the orlistat 30 mg tid, 60 mg tid, 120 mg tid, and 240 mg tid groups, respectively. There was no appreciable change in the amount of fecal fat excreted by the placebo-treated group (-0.1 g/day).

APPEARS THIS WAY ON ORIGINAL

PHARMACOKINETIC RESULTS:

After 24 weeks of treatment, plasma concentrations of orlistat were either non-measurable or detected at the assay's limit of quantification. This confirms that the overall absorption of orlistat is extremely low. There was, however, a dose-related increase in plasma concentrations of both intact orlistat (as evidenced by the percent of samples with measurable concentrations of orlistat) and orlistat's primary metabolite (M1).

CONCLUSIONS:

Orlistat administered at doses of 30 mg tid, 60 mg tid, 120 mg tid and 240 mg tid for 24 weeks produced a dose-dependent body weight loss compared to placebo. Although 60 mg tid produced a statistically significant loss, both the 120 mg and 240 mg dose provided for a greater effect in both the least squares mean difference and the categorical response. There was also a similar effect regarding the secondary efficacy parameters, particularly serum total and LDL-cholesterol. Of the effective doses, the safety profile of the 240 mg tid dose was the least well tolerated with the greatest number and more severe gastrointestinal adverse events possibly related to orlistat as well as have the greatest effect on reduction of fat soluble vitamins. The 60 mg and the 120 mg dose were comparable in their effect on fat soluble vitamins. Based on the results of this study, the dose of orlistat that provided the greatest clinical effect with the best overall safety profile was the 120 mg dose.

Reviewer's Comments: Assay sufficiently validated. [redacted]

Summary of plasma concentrations of orlistat, M1, and M3 from BM14150

Dose	No. of	Ro 18-0647 (Orlistat)		Ro 42-3988 (M1)		Ro 42-2556 (M3)	
(mg tid)	Sample	No. of Measurable[a]	% of Measurable	Mean (N)	CV%	Mean (N)	CV%
0 (placebo)	90	0	0	-	-	-	-
30	87	7 (0.33 - 2.28)	8	-(2)[b]			
60	85	15 (0.20 - 1.72)	18	7.2 (84)	62	49.5 (80)	63
120	96	37 (0.21 - 4.66)	38	13.9 (84)	77	55.0 (82)	62
240	91	56 (0.22 - 8.77)	62	21.6 (94)	67	68.9 (91)	60
				38.8 (89)	81	88.7 (88)	63

[a] With concentration range (ng/mL) in ().

[b] Concentrations were 0.36 and 6.22 ng/mL in these two samples.

[redacted]
APPEARS THIS WAY ON ORIGINAL

Appendix 1.2.2. **Synopsis of Research Report N-138540 (Protocol BM14119B)**

COMPANY: Hoffmann-La Roche Inc. NAME OF FINISHED PRODUCT: XENICAL™ NAME OF ACTIVE INGREDIENT: ORLISTAT	INDIVIDUAL STUDY TABLE REFERRING TO PART ... OF THE DOSSIER: Volume:..... Page:	(FOR NATIONAL AUTHORITY USE ONLY)

INDICATION	Obesity
CLINICAL PHASE	III
DRUG/TITLE OF THE STUDY	Final Study Report - Protocol BM14119B: The efficacy and tolerability of orlistat (120 mg tid) in the treatment of obesity after 52 weeks of therapy. Research Report N-138540 / July 1, 1996
INVESTIGATOR(S)	[redacted]
INSTITUTION	
PUBLICATION	None
PERIOD OF TRIAL	1 June 1992 - 25 August 1994
OBJECTIVES	- To determine if obese patients on a hypocaloric diet lose more weight when treated with 120 mg tid of orlistat than when treated with placebo tid. - To determine the tolerability of 120 mg tid of orlistat when administered for 52 weeks.
STUDY DESIGN	Multicenter, double-blind, placebo-controlled, randomized, parallel group study with a 4-week placebo lead-in period followed by 52 weeks of active treatment.

NUMBER OF SUBJECTS

	Entered Placebo Lead-in	Randomized	Evaluated for Safey	Efficacy	No. Pemature discont For AEs	For othe reasons	death
	267						
Placebo		114	110	108	7	41	0
120 mg olistat		114	112	110	9	32	0

DEMOGRAPHIC DATA (Safety Population)

	Place	120 mg olistat
N	110	112
Sex (M/F)	13/97	13/99
Age (yr)-Mean±SD	41.4±9.9	41.7±10.5
Range	21.0-65.0	19.0-71.0
Weight (kg) Mean±SD	98.4±14.9	98.1±13.4
BMI (kg/m^2) Mean±SD	36.7±3.7	36.6±3.6

TRIAL DRUG / STROKE (BATCH) NOs	120 mg orlistat/Ro 18-0647/090 (Batch Nos. PT 2157 T01, PT 2157 T06, PT 2157 T16)
DOSE/ROUTE/REGIMEN / DURATION	orlistat 120 mg tid/oral/three times daily/52 weeks
REFERENCE DRUG / STROKE (BATCH) NOs	Placebo/Ro 18-0647/098 (Batch Nos. PT 2160 T01, PT 2160 T02, PT 2160 T03, PT2160 T14)
DOSE/ROUTE/REGIMEN / DURATION	placebo/oral/tid/56 weeks
ANALYTICAL METHODS	ANOVA or ANCOVA for changes in body weight and secondary efficacy parameters.

PROCEDURE: Patients fulfilling the inclusion criteria were stabilized during a 4-week single-blind placebo lead-in period on a hypocaloric diet with 30% of calories as fat. On day one they were randomly assigned to receive placebo tid or 120 mg of orlistat tid. Treatment was double-blind and given during meals for 52 weeks.

EFFICACY RESULTS: After one year of treatment with 120 mg tid of orlistat, patients kept off an average of 8.5% of their initial body weight compared with 5.4% for placebo-treated patients. The least squares mean (LSM) difference from placebo in weight loss was statistically significant (p=0.016; 2.0 kg difference). Twenty-eight percent of orlistat-treated patients, but only 17% of placebo-treated patients in the ITT population lost more than 10% of their initial body weight. Conversely, 21% of placebo-treated patients gained up to 5% of their initial body weight by the end of one year, while only 12% of orlistat-treated patients did so.

Over the 52 weeks of double-blind treatment, orlistat-treated patients had statistically significant ($p<0.05$) improvements in LSM levels of total cholesterol, LDL-cholesterol, and the LDL/HDL ratio compared with placebo-treated patients. Among patients with elevated levels at baseline, the effects were even more pronounced, with larger differences and important mean decreases seen among orlistat-treated patients.

There was a trend for improvement in blood pressure, fasting insulin, and to a lesser extent, in fasting glucose levels associated with weight loss in both treatment groups. There was no difference between treatment groups in the waist to hip ratio.

There was a statistically significant ($p<0.05$) difference in the quality of life assessment of satisfaction with treatment among orlistat-treated patients compared with placebo-treated patients. There were no statistically significant differences between treatment groups with respect to overweight distress or depression.

SAFETY RESULTS: Adverse events were mild to moderate in intensity in both treatment groups. The majority of adverse events were judged by the investigator to be unrelated or remotely related to treatment. With the exception of the gastrointestinal (GI) system, the adverse events profile was similar for orlistat and placebo treated groups. A total of 56% of placebo- and 82% of orlistat-treated patients had GI adverse events. GI adverse events that occurred with considerably greater frequency among orlistat-treated patients and could be considered potentially related to the pharmacological effect of orlistat included fatty/oily stool (2.7% of placebo patients, 30% of orlistat patients), liquid stools (14% of placebo patients and 26% of orlistat patients), oily evacuation (2.7% of placebo patients, 22% of orlistat patients), increased defecation (6.4% of placebo patients, 19% of orlistat patients), stools soft (8% of placebo patients, 19% of orlistat patients), fecal urgency (4% of placebo patients, 13% of orlistat patients), feces discolored (0% of placebo patients, 10% of orlistat patients), oily spotting (0% of placebo patients, 9% of orlistat patients), flatus with discharge (1% of placebo patients, 6% of orlistat patients), and fecal incontinence (0% of placebo patients, 5% of orlistat patients). The majority of patients in both treatment groups had only one or two episodes of GI adverse events, including those potentially related to the pharmacologic effect of orlistat.

Seven placebo- and nine orlistat-treated patients withdrew prematurely from the study because of adverse events. Three orlistat-treated patients withdrew because of GI adverse events (one patient each for abdominal pain, liquid stools, and increased defecation). One placebo-treated patient withdrew because of a GI adverse event (esophagitis).

Serious adverse events were uncommon during this one-year study (10 placebo- and 7 orlistat-treated patients). Only one orlistat- and one placebo-treated patient had a serious adverse event in the GI system, neither of which were among those considered potentially related to the pharmacologic effect of orlistat (abdominal pain for the orlistat-treated patient and esophagitis for the placebo-treated patient).

Laboratory abnormalities occurred sporadically, few were judged clinically significant in either treatment group.

Mean levels of vitamins A, D, and E and beta carotene were within normal ranges throughout the study in both treatment groups. The difference from placebo in the least squares mean change in vitamin levels after 52 weeks of treatment was statistically significant ($p<0.001$) among orlistat-treated patients for vitamin E and beta carotene, but not for vitamins A or D. There was no statistically significant change from placebo in the vitamin E/cholesterol ratio. Since orlistat inhibits absorption of ingested fat by about 30%, it is unlikely that either these vitamins or beta carotene would be preferentially inhibited to a greater extent than that.

Among patients with normal ECG results at the start of double-blind treatment, 3% of placebo patients and 7% of orlistat patients had abnormal changes at the end of treatment. None of the changes was considered by the investigator to be clinically meaningful.

New abnormalities in gallbladder ultrasound results were detected at the end of the study in 7% of orlistat- and 11% of placebo-treated patients. New abnormalities in renal ultrasound results were detected at the end of the study in 3% of orlistat- and 2% of placebo-treated patients. The development of gallstones or renal stones was not increased by orlistat use.

PHARMACODYNAMIC RESULTS: After 52 weeks of treatment, mean fecal fat excretion was increased by 16 g/day in orlistat-treated patients. There was no change in fecal fat excretion among placebo-treated patients.

PHARMACOKINETIC RESULTS: At week 24, plasma concentrations of orlistat were either non-measurable (94.4%) or near the assay limit (5.6%). No orlistat was detected in the plasma of either orlistat- or placebo-treated patients after 52 weeks of treatment.

CONCLUSIONS: Orlistat at a dose of 120 mg tid in conjunction with a hypocaloric diet, produced a statistically significant and clinically meaningful reduction in body weight during 52 weeks of treatment compared with placebo treatment. Among orlistat-treated patients there was a significant reduction in total cholesterol, LDL-cholesterol, and LDL/HDL compared with placebo. There was a statistically significant difference from placebo for orlistat patients in satisfaction with treatment in the quality of life assessment. There were positive trends in changes in fasting insulin and blood pressure. In general, orlistat was well tolerated by the obese patients in this study. Systemic absorption of orlistat was extremely low.

Reviewer's Comments: Assay sufficiently validated. [redacted]

Summary of plasma concentrations of orlistat from BM14119B

Treatment	No. Samples Assayed		No. Samples with Measurable Orlistat	
	24 weeks	52 weeks	24 weeks	52 weeks
Placebo	86	72	0	0
Orlistat	89	76	5[a]	0

[a] Concentrations were: 0.35, 0.39, 0.26, 0.28, and 0.31 ng/mL.

[redacted]
APPEARS THIS WAY ON ORIGINAL

Appendix 1.2.3. Synopsis of Research Report N-138721 (Protocol BM14119C)

COMPANY: Hoffmann-La Roche Inc. NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT:	INDIVIDUAL STUDY TABLE REFERRING TO PART .... OF THE DOSSIER: Volume: ..... Page:	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY/REPORT NO./ DATE OF REPORT	Final Study Report - Protocol BM14119C: The efficacy and tolerability of orlistat in the treatment of obesity after 104 weeks of therapy. Research Report N-138721 / October 30, 1996.
INVESTIGATOR(S) / CENTER(S)	[redacted]
PUBLICATION	None
PERIOD OF TRIAL	May 14, 1992 - October 9, 1995 CLINICAL PHASE III
OBJECTIVES	1. To determine the weight loss effect of 120 mg orlistat tid compared to placebo tid over a 1 year period when prescribed with a hypocaloric diet. 2. In a second year of treatment, the ability of orlistat to maintain body weight was assessed as follows: (a) In patients treated with orlistat and hypocaloric diet for the first year: to determine during the second year, the effect on body weight change of 120 mg orlistat tid compared to placebo tid when prescribed with weight maintenance diet. (b) In patients treated with placebo and hypocaloric diet for the first year: to determine during the second year, the effect on body weight change of 120 mg orlistat tid compared to placebo tid when prescribed with weight maintenance diet. 3. To determine the tolerability of 120 mg orlistat tid administered orally for either 52 or 104 weeks.
METHODOLOGY	Multicenter, double-blind, placebo-controlled, randomized parallel-group study with a 4-week placebo-lead in period followed by 104 weeks of active treatment.

NUMBER OF SUBJECTS

YEAR ONE

Entered Placebo Lead-in		Randomized	Evaluated for Safety	Evaluated for Efficacy	Withdrawn due to AEs	Withdrawn due to Death	Withdrawn due to Other
743	PLA	343	340	340	9	-	74
	120 mg	345	343	343	23	-	38

YEAR TWO

Entered Second Year	Randomized		Evaluated for Safety	Evaluated for Efficacy	Withdrawn due to AEs	Withdrawn due to Death	Withdrawn due to Other
PLA	PLA/PLA	126	124	123	3	-	21
1st year 253	PLA/120 mg	127	124	124	6	-	19
120 mg	120 mg/PLA	138	138	138	4	-	17
2nd year 273	120 mg/120 mg	135	133	133	3	1	17

DEMOGRAPHIC

YEAR ONE

	Total	Placebo	120 mg
N	683	340	343
Sex (M/F)	116/567	57/283	59/284
Age (Yr) - Mean±SD	44.8±11.0	44.3±11.2	45.2±10.9
Range	18.0-77.0	18.0-77.0	20.0-76.0
Weight (Kg) Mean±SD	99.5±14.6	99.8±14.2	99.1±15.1
Bmi (Kg/M^2) Mean±SD	36.1±3.8	36.0±3.9	36.1±3.9

YEAR TWO

	Total	PLA/PLA	PLA/120 MG	120 MG/PLA	120/120 MG
N	519	124	124	138	133
Sex (M/F)	93/426	23/101	22/102	21/117	27/106
Age (Yr) - Mean±SD	45.9±10	45.8±9.8	45.1±11.1	47.1±10.0	45.3±11.2
Range	20.0-76	21.0-67.0	20.0-71.0	20.0-76.0	21.0-72.0
Weight (Kg) Mean±SD	91.2±15.3	92.6±14	93.2±15.6	90.0±15.9	

TRIAL DRUG / STROKE (BATCH) NOs
DOSE / ROUTE / REGIMEN / DURATION

120 mg orlistat / Ro 18-0647/090 (Batch No. PT 2157 T 24, PT 2157 T 25, PT 2157 T 31, PT 2157 T 32, PT 2157 T 33, PT 2157 T 34, PT 2157 T 35, PT 2157 T 36, PT 2157 T 37, PT 2157 T 41) / Orlistat / Oral / tid / 104 weeks

REFERENCE DRUG / STROKE (BATCH) NOs
DOSE / ROUTE / REGIMEN / DURATION

Placebo / Ro 18-0647/098 (Batch No. PT 2160 T 15, PT 2160 T 16, PT 2160 T 17, PT 2160 T 24, PT 2160 T 25, PT 2160 T 31) / Placebo / oral / tid / 104 weeks

STATISTICAL METHODS

ANOVA or ANCOVA for changes in body weight and secondary efficacy parameters

PROCEDURE

[redacted]

Patients fulfilling the inclusion criteria were stabilized during a 4-week single blind placebo lead-in period on a hypocaloric diet with 30% of calories as fat. On day one they were randomly assigned to receive placebo tid or 120 mg of orlistat tid for 52 weeks. After 52 weeks of double-blind treatment, patients received an additional 52 weeks of double-blind treatment of orlistat or placebo along with a weight maintenance (eucaloric) diet (a diet designed to facilitate body weight maintenance and helped prevent weight regain).

EFFICACY RESULTS

During the first year of double-blind treatment patients in the orlistat group lost their weight more rapidly and for longer period of time than patients in the placebo group. At the end of week 52, the orlistat patients lost 10.2% of their initial body weight, while placebo patients lost only 6.1%. The difference between both treatment groups was statistically significant ($p<0.05$). There was a tendency to regain some of the lost weight during the second year of treatment in all treatment groups, with exception of the PLA/120 mg treatment group where patients continued to lose weight until at the end of week 104 they had a lost an additional 0.9 kg 15% of the weigh losst. Patients in the 120 mg/120 mg, 120 mg/PLA, and PLA/PLA regain 26%, 52%, and 40% of the lost weight, respectively. The highest percentage of patients who did not regain any weight during the second year of treatment after they lost 5% of their initial body weight during the first year of treatment was seen in the PLA/120 mg group (51.5%), followed by 120 mg/120 mg group (28.4%), PLA/PLA group (21.9%) and 120 mg/PLA group (4.6%). During the two years of the same treatment (120 mg/120 mg or PLA/PLA), at least as twice as many orlistat-treated patients lost >10 % of initial body weight compared to placebo-treated patients (33.8% vs 14.6%, respectively). The least squares mean difference was statistically significant for orlistat treatment group which indicates that the effect of orlistat was maintained throughout two years of treatment ($p< 0.05$).

After one year of treatment, there was a statistically significant reduction in the least square mean levels of total cholesterol, LDL-cholesterol and LDL/HDL ratio ($p<0.05$) in orlistat treatment group compared to placebo group. Patients who received placebo during the first year of treatment but continued on orlistat during the second year (PLA/120 mg), showed statistically significantly lower total cholesterol, LDL-cholesterol and HDL-cholesterol values ($p<0.05$) compared to patients who received placebo during the second year (PLA/PLA). Statistically significant reduction in the least squares mean levels of total cholesterol and LDL-cholesterol was also seen in patients who received orlistat treatment during the first year and who continued on orlistat treatment during the second year (120 mg/120 mg), compared to patient in the 120 mg/PLA treatment group ($p<0.05$%), after the two years of the same treatment, the least squares mean difference from the PLA/PLA treatment group were evident for the 120 mg/120 mg treatment group for total cholesterol, LDL-cholesterol, VLDL-cholesterol and LDL/HDL ratio ($p<0.05$).

During the first year of treatment, both systolic and diastolic blood pressures were statistically significantly lower for the orlistat-treated patients ($p<0.05$). However, no statistically significant differences between the orlistat and the placebo treatment groups were seen during the second year of either orlistat or placebo treatment. The improvement was seen in lower fasting glucose values for patients treated with orlistat during the first year and during the two full years of orlistat treatment ($p<0.05$). After 52 weeks of treatment the waist circumference was reduced more in orlistat patients than in placebo patients. Despite the waist circumference increase in all treatment groups during the second year of treatment, patients treated with orlistat for two years showed greater waist circumference reduction than patients treated with placebo for two years. Improvement in certain quality of life assessments was also observed in orlistat-treated patients. There was a statistically significant difference in patient ratings of satisfaction with treatment index in the orlistat treatment groups during the year one (120 mg) and during two years of the same treatment (120 mg/120 mg) compared to the placebo treatment groups (PLA) and (PLA/PLA) ($p<0.05$).

SAFETY RESULTS

Adverse events were generally mild or moderate in all treatment groups and resolved without intervention. While the total percentage of patients reporting adverse events in this study was large, differences between the orlistat and placebo groups were small, except for adverse events of a gastrointestinal nature. Gastrointestinal adverse events that occurred with considerably greater frequency among orlistat-treated patients and could be considered potentially related to the pharmacologic effect of the drug included fatty/oily stools, increased defecation, oily spotting, soft stools, fecal urgency, flatulence, flatus with discharge, fecal incontinence, and oily evacuation. During year one, 78.4% and 52.1% of patients treated with orlistat or placebo, respectively, experienced at least one GI adverse event. During the second year there were 42.1%, 36.2%, 29.8% and 70.4% of patients in the 120 mg/120 mg, 120 mg/PLA, PLA/PLA and PLA/120 mg treatment groups, respectively, who experienced one or more GI adverse event. There were 82.7% and 60.5% of patients who received two years of either orlistat or placebo treatment, respectively, who reported at least one GI adverse event. Most patients reporting adverse events while receiving orlistat had only one or two episodes of the event, and the majority of the gastrointestinal events were judged to be mild or moderate in intensity. A total of 23 (6.7%) patients in the orlistat group and 9 (2.6%) in the placebo group discontinued from the study prematurely because of an adverse event during the year one. The number of patients discontinued from the study during the second year of double-blind treatment was low for all treatment groups: 3 (2.3%), 4 (2.9%), 2 (1.6%), and 6 (4.8%) of patients in the 120 mg/120 mg, 120 mg/PLA, PLA/PLA, and PLA/120 mg, treatment groups, respectively. Total number of patients who discontinued from the study during the two years of the same either orlistat or placebo treatment was 3 and 2, respectively. Serious adverse events were uncommon during year one, year two, and two years of the same treatment, and most of them were considered to be either unrelated or remotely related to treatment. There were two deaths reported during the study, both considered to be unrelated to treatment. Patient No. 7571[redacted] (120 mg/120 mg treatment group), died of cardiac arrest, and patient No. 11943[redacted] (120 mg/PLA treatment group), died due to an automobile accident.

Most laboratory abnormalities, other than changes in vitamin levels, occurred sporadically and there were no clinically significant changes in the mean values of any laboratory parameters during the year one, year two, and two years of the same treatment. Mean levels of vitamin A, D, and E, and beta-carotene remained within the normal ranges throughout the study in all treatment groups. However, the least squares mean differences from placebo in vitamin D, E, and beta-carotene were statistically significant in orlistat treatment groups in year one (120 mg), year two (PLA/120 mg) and two years of the same treatment (120 mg/120 mg) ($p < 0.05$). In the 120 mg/PLA treatment group only vitamin E and beta-carotene were statistically significantly different from the placebo treatment group ($p < 0.05$).

Orlistat treatment had no clinically significant effect on pulse rate or electrocardiogram results. The development of gallstones or renal stones did not appear to be increased by chronic orlistat administration for two years.

PHARMACODYNAMICS

After 24 and 52 weeks of treatment with orlistat, mean fecal fat values increased from the start of double-blind treatment by 24 g/day and 21 g/day, respectively. As expected, there was almost no change in the amount of fecal fat excreted by the placebo-treated group after either 24 or 52 weeks of treatment.

PHARMACOKINETICS

Systemic exposure of orlistat at the 120 mg tid dose level for 24, 52, and 104 weeks treatment in obese patients was extremely low without any evidence of accumulation.

CONCLUSION

Orlistat administered at a dose of 120 mg tid in conjunction with a mildly hypocaloric diet, produced a statistically significant and clinically meaningful reduction in body weight after one year of treatment compared with placebo treatment. A significantly greater amount of weight loss was maintained for longer periods of time over the two years of orlistat treatment. Orlistat also prevented much of the regain of body weight that inevitably occurs after a patient initially losses weight, especially when the patients' diet changes after an initial weight loss.

In addition to the effect on body weight, treatment with orlistat produced meaningful improvements in secondary efficacy parameters associated with potential increased risk of increased morbidity or early mortality. Especially significant are long term improvement of total cholesterol, LDL cholesterol, the LDL/HDL ratio, fasting glucose, fasting insulin and diastolic blood pressure. In patients with a pre-existing higher risk, the effects are even greater. In general orlistat treatment was well tolerated during chronic treatment. When compared to placebo there were also overall improvements in many aspects of the patients quality of life.

Reviewer's Comments: Assay sufficiently validated. [redacted]

Summary of plasma concentrations of orlistat from BM14119C

Treatment	No. Samples Assayed			No. Samples with Measurable Orlistat		
	24 weeks	52 weeks	104 weeks[a]	24 weeks	52 weeks[b]	104 weeks[a]
Placebo	259	225	152	2	2	0
Orlistat	281	236	141	13	17	2

[a] Second year data were after re-randomization following one year of treatment.

[b] Excluded samples from site CRTN 11945 (13 placebo- and 15 orlistat-treated samples) because of sample handling errors.

Appendix I.2.4. Synopsis of Research Report N-138870 (Protocol NM14161)

COMPANY: Hoffmann-La Roche Inc. NAME OF FINISHED PRODUCT: Xenical™ NAME OF ACTIVE INGREDIENT: TETRAHYDROLIPSTATIN	INDIVIDUAL STUDY TABLE REFERRING TO PART ... OF THE DOSSIER: Volume: ..... Page:	(FOR NATIONAL AUTHORITY USE ONLY)

TITLE OF THE STUDY/REPORT NO./ DATE OF REPORT	Final Study Report – Protocol NM14161: The efficacy and tolerability of orlistat (60 mg and 120 mg tid) in the treatment of obesity after 104 weeks of therapy. Research Report N-138870 / October 3, 1996.
INVESTIGATOR(S) / CENTER(S)	[redacted]
PUBLICATION	None
PERIOD OF TRIAL	26 February 1993 - 1 December 1995 CLINICAL PHASE III
OBJECTIVES	- To determine the long-term weight control effect of 120 mg orlistat, 60 mg orlistat, or placebo (all administered tid) in combination with dietary counseling for two years in a primary care setting. - To determine the weight loss effect of 120 mg orlistat, 60 mg orlistat, or placebo (all administered tid) in combination with a mildly hypocaloric diet during the first year of treatment. - To determine the long-term tolerability of orlistat 120 mg or 60 mg given three times a day with meals to obese patients for 104 weeks.
STUDY DESIGN	Multicenter, double-blind, randomized, parallel-group, double-dummy, placebo-controlled with a 4-week placebo lead-in period followed by 104 weeks of active treatment.

NUMBER OF SUBJECTS

[redacted]

	Entered Placebo Lead-in	Randomized	Evaluated for Safety	Evaluated for Efficacy	No premature discont for AEs	No premature discont for Other	No premature discont for Death
	796						
Placebo		214	212	212	15	108	0
60 mg orlistat		214	213	213	14	80	0
120 mg orlistat		214	210	210	23	73	1

DEMOGRAPHIC DATA

	Placebo	60 mg orlistat	120 mg orlistat
N	212	213	210
Sex (M/F)	47/165	47/166	44/166
Age (yr) - Mean±SD	41.6±9.6	42.6±11.0	43.2±10.1
Range	18-71	20-72	18-78
Weight (kg) Mean±SD	101.8±14.6	100.4±14.6	100.5±14.2

[redacted]

TRIAL DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	Orlistat 60 mg/Ro 18-0647/0102 Orlistat 120 mg/Ro 18-0647/090
DOSE / ROUTE / REGIMEN / DURATION	Orlistat 60 mg or 120 mg/oral/tid/104 weeks
REFERENCE DRUG / STROKE (BATCH) NOs	Placebo for 60 mg capsules/Ro-18-0647/0103; Placebo for 120 mg capsules/Ro-18-0647/098
DOSE / ROUTE / REGIMEN / DURATION	Placebo/oral/tid/108 weeks
ANALYTICAL METHODS	ANCOVA for changes in body weight and secondary efficacy parameters.

PROCEDURE:

Patients fulfilling the inclusion criteria were stabilized during a 4-week single-blind placebo lead-in period on a mildly hypocaloric diet with 30% of calories as fat. On day 1 they were randomly assigned to receive either placebo tid, 60 mg orlistat tid, or 120 mg orlistat tid. Treatment was double-blind and given during meals for 104 weeks. After 52 weeks of double-blind therapy, patients were placed on a eucaloric diet and maintained on the same treatment regimen.

EFFICACY RESULTS:

After one year of double-blind treatment, weight loss in patients treated with 60 mg orlistat or 120 mg orlistat averaged a 7.1% and 7.9% decrease from initial body weight compared with a 4.2% decrease in the placebo group. Among patients who completed one year of treatment, 59% of those in the 60 mg orlistat group and 62% of those in the 120 mg orlistat group lost more than 5% of their initial body weight by week 52 compared with 43% of those in the placebo group. As expected there was a tendency in the second year of treatment when patients were switched to a eucaloric diet to regain some of the weight lost during the first year. However, patients in the 60 mg and 120 mg orlistat groups maintained a weight loss of 4.4% and 5.0%, respectively, at the end of year two. In contrast, by week 104, patients in the placebo group had regained most of their weight (average weight loss of 1.7%). Forty three percent of the patients who completed two years of treatment with 60 mg or 120 mg orlistat maintained a weight loss of more than 5% of their initial body weight compared to those who completed two years of placebo treatment (30%). The least squares mean difference in weight loss from placebo was statistically significant at week 52 for both orlistat treatment groups; statistical separation in the amount of weight lost in the orlistat and placebo groups was evident. The least squares mean difference from placebo in weight loss at week 104 was also statistically significant for both orlistat treatment groups indicating that the effect of orlistat was maintained throughout two years of treatment ($p \leq 0.001$).

After 52 weeks of treatment, there was a statistically significant reduction in the least squares mean levels of total cholesterol and LDL-cholesterol in the two orlistat treatment groups compared with placebo ($p \leq 0.001$) as well as statistically significant increases in HDL-cholesterol in the 60 mg orlistat group relative to placebo ($p=0.022$). Furthermore, although these lipid levels tended to increase in all groups from week 52 to week 104, the average increase in LDL cholesterol at week 104 was significantly less in the 60 mg and 120 mg orlistat groups compared to placebo.

Patients treated with 120 mg orlistat had significantly greater reductions in fasting insulin at week 52 compared to placebo. Insulin levels remained reduced in both orlistat groups during the second year of treatment. Two years of treatment with 60 mg tid or 120 mg tid orlistat had no adverse effects on fasting glucose values or on patients' response to an oral glucose challenge. The least squares mean differences in the changes in diastolic blood pressure relative to placebo were statistically significant for patients in both orlistat treatment groups who completed 104 weeks of treatment ($p<0.05$). Improvement in certain quality of life assessments was also observed. There was a statistically significant difference in patient ratings of satisfaction with treatment index in the two orlistat treatment groups compared to the placebo group at weeks 52 and 104 ($p \leq .0002$).

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SAFETY RESULTS:

Adverse events were generally mild or moderate in intensity in all three treatment groups and resolved without intervention. While the total percentage of patients reporting adverse events in this 104-week study was large, differences between the two orlistat and placebo groups were small, except for adverse events of a gastrointestinal nature. Throughout the two years of double-blind treatment, 59%, 72%, and 79% of patients in the placebo, 60 mg orlistat, and 120 mg orlistat groups experienced at least one GI adverse event. Gastrointestinal adverse events that occurred with considerably greater frequency among orlistat-treated patients and could be considered potentially related to the pharmacologic effect of the drug included fecal urgency, fecal incontinence, fatty/oily stool, oily evacuation, flatus with discharge, liquid stools, and increased defecation. Most patients in the orlistat treatment groups reporting gastrointestinal adverse events had only one or two episodes of the event, and the majority of the gastrointestinal adverse events were judged to be mild or moderate in intensity. A total of 15 (7%) patients in the placebo group, 14 (7%) in the 60 mg orlistat group, and 23 (11%) in the 120 mg orlistat group discontinued the study prematurely because of an adverse event(s). In the 60 mg and 120 mg orlistat treatment groups, 10 (4.7%) and 12 (5.7%) of these patients, respectively, withdrew for gastrointestinal adverse events compared to 3 (1.4%) placebo patients. Serious adverse events were uncommon during this two-year study, and most of them were considered to be either unrelated or remotely related to treatment. A 55-year old male in the 120 mg orlistat group died of an acute myocardial infarction. The death was considered unrelated to treatment by the investigator and remotely related to treatment by the sponsor.

Most laboratory abnormalities, other than changes in vitamin levels, occurred sporadically and few were judged to be clinically relevant in any of three treatment groups. Mean levels of vitamin A, D, and E, and beta-carotene were within the normal ranges throughout the study in all treatment groups. The difference from placebo in the least squares mean change in vitamin levels after 104 weeks of treatment was statistically significant or approached significance in the two orlistat treatment groups for vitamin D and beta-carotene ($p \leq 0.058$), but not for vitamins A and E. Moreover, the vitamin E/total cholesterol ratio at year two did not differ between the orlistat and placebo groups, although the beta carotene/cholesterol levels were significantly lower in the two orlistat groups compared to the placebo group ($p \leq 0.077$). Only a small number of patients in the three treatment groups had values of vitamins A, D or E, or beta carotene that fell below the lower limit of the reference range at any time during the two year study. Over the two years of double-blind treatment, few patients received vitamin supplementation of which most received supplementation for low vitamin D and beta-carotene levels.

Orlistat treatment had no clinically relevant effect on pulse rate or electrocardiogram results. The development of gallstones or renal stones did not appear to be increased by chronic orlistat administration for two years.

PHARMACODYNAMICS:

After 52 and 104 weeks of orlistat administration, mean fecal fat excretion was increased from the start of double-blind treatment by approximately 16 g/day in the 60 mg group and by 21 g/day in the 120 mg group. As expected, there was little change in the amount of fecal fat excreted by placebo-treated patients at these timepoints. These results indicate that the pharmacologic effect of orlistat is maintained over 2 years.

PHARMACOKINETICS:

Systemic absorption of orlistat was extremely low during the study, although the number of samples that contained measurable orlistat was approximately proportional to the dose level. Plasma concentrations of the inactive primary (M1) and secondary (M3) metabolites of orlistat were higher than the parent compound at all timepoints; M1 levels were proportional to the dose of orlistat. No further accumulation was evident for either orlistat or its metabolites from six months to either one or two years of continued administration.

CONCLUSIONS:

Orlistat, administered at a dose of 60 or 120 mg tid in conjunction with a mildly hypocaloric diet in a primary care setting and without the use of extensive dietary or behavioral counseling, produced a statistically significant and clinically meaningful reduction in body weight after one year of treatment compared with placebo treatment, and this significantly greater weight loss was maintained during the second year of continued treatment. In general, chronic administration of 60 or 120 mg of orlistat for up to two years was well tolerated by obese patients, however, greater improvement was showed with 120 mg of orlistat.

Reviewer's Comments: Assay sufficiently validated. (RMS)

Summary of plasma orlistat, M1, and M3 pharmacokinetics for protocol NM14161

Time (weeks)	Percent Measurable/Total N of Samples Assayed for Orlistat[a]		Mean Plasma Concentration (ng/mL)[b]			
			M1 (Ro 42-3988)		M3 (Ro 42-2556)	
	60 mg	120 mg	60 mg	120 mg	60 mg	120 mg
20	28%/181 (0.20-4.32)	41%/184 (0.20-4.66)	16.7 (85) : 100%/71	26.4 (69) : 100%/75	85 (65) : 89%/17	133 (78) : 79%/23
48	24%/157 (0.20-3.50)	52%/145 (0.22-5.11)	14.8 (80) : 100%/64	27.1 (75): 100%/78	83 (55) : 95%/19	98 (60) : 88%/28
100	19%/114 (0.23-1.96)	43%/115 (0.21-3.86)	15.9 (98) : 95%/19	24.6 (90) : 100%/29	86 (53) : 72%/13	92 (55) : 93%/27
Average	*23.8 (N=452)*	*45.0 (N=444)*	*15.8 (N=154)*	*26.3 (N=182)*	*85 (N=47)*	*108 (N=78)*

[a] Concentration range (ng/mL) in ().
[b] Mean (CV%) : Percent Measurable/Total N of Samples Assayed

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Appendix 1.2.5. Synopsis Of Research Report N-138826 (Protocol NM14336)

COMPANY: Hoffmann-La Roche Inc. NAME OF FINISHED PRODUCT: NAME OF ACTIVE INGREDIENT:	INDIVIDUAL STUDY TABLE REFERRING TO PART .... OF THE DOSSIER: Volume: ..... Page:	(FOR NATIONAL AUTHORITY USE ONLY)

INDICATION	Obesity
CLINICAL PHASE	III
TITLE OF THE STUDY/REPORT NO./ DATE OF REPORT	Final Study Report - Protocol NM14336: A 57-Week Study of the Effect of Orlistat in the Treatment of Obese Subjects with Non-Insulin Dependent Diabetes Mellitus (NIDDM) Maintained on Oral Hypoglycemic Agents. Research Report N-138826 / September 13, 1996.
INVESTIGATOR(S) / CENTER(S)	[redacted]
PUBLICATION	None
PERIOD OF TRIAL	December 21, 1993 - January 4, 1996
OBJECTIVES	Primary: To determine the long-term weight loss effect in obese NIDDM patients maintained on oral hypoglycemic agents treated for 52 weeks with orlistat 120 mg tid or placebo in conjunction with a hypocaloric diet and behavioral counseling. Secondary: To determine if obese patients with NIDDM treated with orlistat 120 mg tid plus a hypocaloric diet require a change in the dosage of the oral hypoglycemic medication. Secondary: To determine if obese patients with NIDDM treated with orlistat 120 mg tid plus a hypocaloric diet have altered glycemic control as compared to those treated with diet plus placebo. Secondary: To determine if obese patients with NIDDM treated with orlistat 120 mg tid plus a hypocaloric diet have a difference in the occurrence of hypoglycemic episodes. Secondary: To determine the long-term tolerability of 120 mg orlistat given tid with meals to obese patients.

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Appendix 1.2.5. Synopsis Of Research Report N–138826
(Protocol NM14336)

STUDY DESIGN	Multicenter, double–blind, randomized, placebo controlled, parallel design

NUMBER OF SUBJECTS

	Evaluated for:				No. of premature discont. for:	
	Rand.	Safety	Efficacy (ITT)	AE	Other Reasons	Death
Placebo	159	159	159	23	21	0
120 mg tid	163	162	162	12	12	0

DEMOGRAPHIC DATA
(Safety Population)

	Placebo	120 mg orlistat
N	159	162
Sex (M/F)	85/74	79/83
Age (Yr) - Mean±SD	54.7±9.7	55.4±8.8
Range	27.0-76.0	35.0-73.0
Weight (kg) Mean±SD	99.7±15.4	99.6±14.5
Bmi (kg/m^2) Mean±SD	34.0±3.4	34.5±3.2

DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Body Mass Index (BMI): 28–40, NIDDM treated with any oral hypoglycemic agent for at least 6 months and currently stable on a second generation sulfonylurea: glyburide or glypizide, hemoglobin A1c: 6.5–10%, age: ≥18 years, gender: male or female.
TRIAL DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	120 mg capsules of orlistat Ro 18–0647/090 (C Nos. C171712, C174523, C176183, C176983) 120 mg orlistat/oral/tid/52 weeks
REFERENCE DRUG / STROKE (BATCH) NOs	Placebo Ro 18–0647/098 (C Nos. C172802, C173522, C175063) placebo/oral/tid/52 weeks
STATISTICAL METHODS	Efficacy: The primary efficacy measurement was the change from baseline in body weight at Week 52. The secondary efficacy measurements were the changes from baseline in fasting insulin and glucose, hemoglobin A1c, and lipid levels; changes in oral hypoglycemic medication dosage, blood pressure, and anthropometric measurement; and scores from the quality of life questionnaire. Analysis of covariance and/or variance techniques were performed for between treatment comparison. Safety: Treatment groups were compared using descriptive statistics with respect to the following safety parameters: vital signs, adverse experiences, changes in hypoglycemic episodes and symptoms, electrocardiograms, gallbladder ultrasounds and laboratory tests including plasma levels of vitamins (A, D, E), beta–carotene, and prothrombin time.

PROCEDURES:

Patients meeting the inclusion criteria entered a 5–week single–blind, placebo lead–in period and were placed throughout the trial on a nutritionally balanced weight loss diet based on the American Diabetes Association diet. Following the 5–week single–blind, placebo lead–in period, patients with a fasting glucose of 100–220 mg/dL at Week –1 were randomized to one of the following two groups: Group A received placebo tid for 52 weeks; Group B received 120 mg orlistat tid for 52 weeks. Treatment was administered as one capsule three times a day with meals from Week –5 to Week 52.

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