

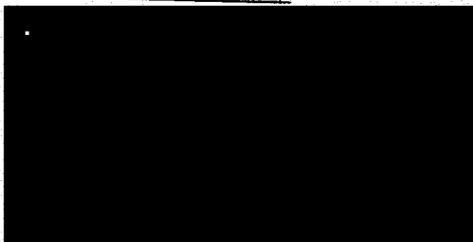
Appendix 1.5.2.3. The Effect Of Xenical™ (Orlistat, Ro 18-0647) on the Pharmacokinetics of Phenytoin in Healthy Volunteers (Protocol NK14574A)

VOLUME: 1.143

OBJECTIVES:

To assess the effect of Xenical™ (orlistat, Ro 18-0647) on the pharmacokinetics of phenytoin (Dilantin® Kapseals®) in healthy volunteers.

INVESTIGATOR/SITE:



FORMULATIONS:

Phenytoin: Extended phenytoin sodium 100-mg capsules (Dilantin® Kapseals®, Parke Davis), lot No. 05384FA

Orlistat: 120-mg capsules (Ro 18-0647/090 batch no. PT2157 T40, clinical order no. C176203-001)

Orlistat Placebo: matching capsules (Ro 18-0647/098, batch no. PT2160 T06, clinical order no. C169121-010)

STUDY METHODS:

(a) Design: Third-party blind, placebo-controlled, randomized, two-way crossover with at least a two-week washout (for phenytoin) period between treatments. A single oral dose of 300 mg phenytoin was administered on two separate occasions: on the fourth day of orlistat 120 mg and placebo tid for 7 days.

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
12/0	20 - 46	67.5 - 94.6	6 White/6 Black

(c) Sampling times:

Day 4: serum samples were collected at 0 h (predose); and 1, 2, 3, 4, 6, 8, 12, 24, 36, 48, 72, and 96 h postdose of phenytoin.

ASSAY:

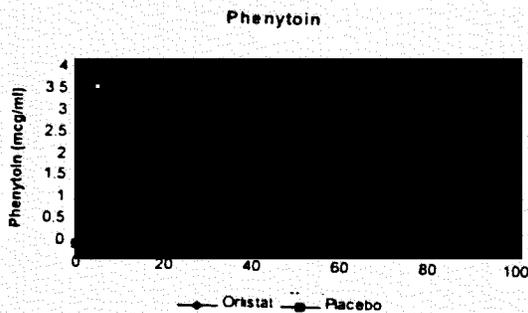
Serum concentrations of phenytoin were assayed by a specific [REDACTED]

### DATA ANALYSIS:

Model independent methods followed by the standard ANOVA for crossover designs, and 90% confidence intervals for parameters.

### RESULTS

Parameter	Orlistat	Placebo
Cmax ( $\mu\text{g/ml}$ )	$3.97 \pm 0.46$	$3.81 \pm 1.8$
AUC(0-t) ( $\mu\text{g}\cdot\text{hr/ml}$ )	$130 \pm 30$	$130 \pm 32$
AUC(0-inf) ( $\mu\text{g}\cdot\text{hr/ml}$ )	$136 \pm 33$	$136 \pm 37$
$\lambda_z$ (1/hr)	$0.045 \pm 0.01$	$0.045 \pm 0.01$
90% CI for Cmax: Orlistat vs. Placebo	1.24 (1.06, 1.44)	
90% CI for AUC(0-inf): Orlistat vs. Placebo	1.00 (0.96, 1.05)	



### CONCLUSION/LABELING CLAIM:

Therapeutic doses of orlistat do not alter the pharmacokinetics of phenytoin in healthy volunteers

### REVIEWER COMMENTS

**BEST POSSIBLE**

1) Assay sufficiently validated.

2) Although sequence effect precludes analysis of Cmax, looking at graph of mean data it is clear there is no effect of orlistat.

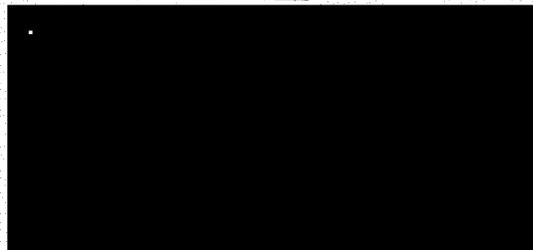
Appendix 1.5.2.4. The Effect of Orlistat (Ro 18-0647) on the Pharmacokinetics and Pharmacodynamics of Warfarin In Healthy Volunteers (Protocol NK14687B)

VOLUME: 1.145

OBJECTIVES:

To assess the effect of orlistat (Ro 18-0647) on the pharmacokinetics and pharmacodynamics of warfarin in healthy volunteers.

INVESTIGATOR/SITE:



FORMULATIONS:

- Warfarin: warfarin sodium 10-mg tablets (Coumadin®, Du Pont Pharmaceuticals)  
lot No. EFN223A
- Orlistat: 120 mg capsules (Ro 18-0647/090, batch no. PT2157 T50,  
clinical order no. C177173-001)
- Orlistat Placebo: matching capsules (Ro 18-0647/098, batch no. PT2160 T32,  
clinical order no. C176803-001)

STUDY METHODS:

(a) Design: Third-party blind, placebo-controlled, randomized, two-way crossover with at least a three-week washout (for warfarin) period between treatments in which a single oral dose of 30 mg warfarin sodium (three 10-mg tablets) was administered on two occasions: on the eleventh day of treatment with orlistat 120 mg and matching placebo tid for 16 days.

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
12/0	24 - 54	61.0 -90.0	7 White
			4 Black
			1 Indian

(c) Sampling times:

PK: Day 4: plasma samples were collected at 0 h (predose); and 0.5, 1, 2, 4, 12, 24, 36, 48, 60, 72, 96, 120, and 144 h postdose of warfarin

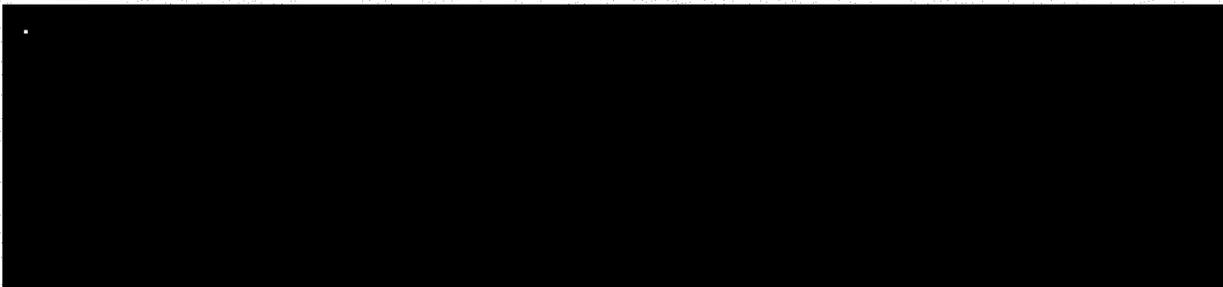
PD (anticoagulation assessment): Days -7 and 1 (Intervals 1 and 2): blood once in the morning after an

overnight fast.

Days 4 - 10: as PK sampling times.

Vitamin K<sub>1</sub>, vitamin K<sub>1</sub> epoxide, osteocalcin, and undercarboxylated osteocalcin: serum samples were collected prior to breakfast on Days -7, 1, 4, 6, and 10.

**ASSAY:**



**DATA ANALYSIS:**

Model independent methods followed by the standard ANOVA for crossover designs and 90% confidence intervals for parameters.

**RESULTS**

Parameter	A <sup>b</sup>	B <sup>b</sup>	C.V. <sup>d</sup> (%)	A/B	90% CI <sup>e</sup> for A/B
<b>R-Warfarin</b>					
C <sub>max</sub> (ng/mL)	1704	1607	9	1.06	0.99, 1.14
t <sub>max</sub> (h)	3.5 <sup>c</sup>	2.5 <sup>c</sup>	37	1.0 <sup>c</sup>	0.2, 1.8 <sup>c</sup>
AUC <sub>0-1</sub> (ng·h/mL)	83858	84722	7	0.99	0.94, 1.04
AUC (ng·h/mL)	92758	93566	8	0.99	0.94, 1.05
λ <sub>z</sub> (h <sup>-1</sup> )	0.0171 <sup>c</sup>	0.0169 <sup>c</sup>	7	0.0002 <sup>c</sup>	-0.0007, 0.0011 <sup>c</sup>
t <sub>1/2</sub> (h) <sup>a</sup>	40.6	41.1			
<b>S-Warfarin</b>					
C <sub>max</sub> (ng/mL)	1617	1598	11	1.01	0.93, 1.10
t <sub>max</sub> (h)	2.8 <sup>c</sup>	2.5 <sup>c</sup>	44	0.3 <sup>c</sup>	-0.5, 1.2 <sup>c</sup>
AUC <sub>0-1</sub> (ng·h/mL)	62081	62061	7	1.00	0.95, 1.06
AUC (ng·h/mL)	66312	66005	7	1.00	0.96, 1.05
λ <sub>z</sub> (h <sup>-1</sup> )	0.0234 <sup>c</sup>	0.0233 <sup>c</sup>	5	0.0001 <sup>c</sup>	-0.0008, 0.0010 <sup>c</sup>
t <sub>1/2</sub> (h) <sup>a</sup>	29.6	29.7			

Vitamin K<sub>1</sub> Nutritional Status Assessment on Day 4, the Eleventh Day of Treatment with Orlistat (A) or with Placebo (B)

Parameter	No. of Subjects	A <sup>b</sup>	B <sup>b</sup>	C.V. <sup>c</sup> (%)	A/B	90% CI <sup>d</sup> for A/B
K <sub>1</sub> (nM/L)	9	0.844	1.214	65	0.69	0.39, 1.25
K <sub>1</sub> ep/K <sub>1</sub> (%)	8	6.891	3.921	80	1.76	0.79, 3.92

CONCLUSION/LABELING CLAIM:

Multiple therapeutic doses of orlistat (120 mg tid) did not alter warfarin pharmacokinetics and pharmacodynamics. Short-term treatment (two weeks) with orlistat does not affect vitamin K nutritional status.

REVIEWER COMMENTS

1) Clearly no effect on warfarin PK, but data suggest that Vit K is adversely affected. Labeling should reflect uncertainty of what effect chronic orlistat has on Vitamin K and PT (INR).

APPEARS THIS WAY ON ORIGINAL

Appendix 1.5.3. Alcohol and Concomitant Medications

Appendix 1.5.3.1. Interaction Study with Orlistat and Ethanol (BD14418)

VOLUME: 1.133

OBJECTIVES:

- Primary: To investigate the possible interference of (1) ethanol on the effect of orlistat on dietary fat absorption and (2) orlistat on the oral pharmacokinetics of ethanol
- Secondary: To investigate the effect of ethanol on plasma levels of orlistat.

INVESTIGATOR/SITE:

[REDACTED]

FORMULATIONS:

Ethanol: 96% (41.7 g/300 mL orange juice) - ethanol was obtained from [REDACTED] mint flavor solution, batch NN-08839, from [REDACTED] and orange juice from [REDACTED]

Orlistat: 120-mg capsules (Ro 18-0647/090, batch no. PT2157 T08)

Orlistat Placebo: matching capsules (Ro 18-0647/098, batch no. PT2160 T31)

STUDY METHODS:

(a) Design: Double-blind (with respect to both orlistat and ethanol), randomized, 3 parallel groups (A, B, C) comprised of 10 subjects each.

Group A: 120 mg orlistat tid on days 1 - 6;  
ethanol placebo qd (lunch) on days -1 and 6, and bid (lunch and dinner) on days 1-5.

Group B: 120 mg orlistat tid on days 1 - 6;  
ethanol qd (lunch) on days -1 and 6, and bid (lunch and dinner) on days 1 to 5.

Group C: 120 mg orlistat placebo tid on days 1 - 6;  
ethanol qd (lunch) on days -1 and 6. and bid (lunch and dinner) on days 1 to 5.

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
30/0	20-30	63.7-105.5	27 White
			3 other

(c) Sampling times:

Ethanol: Plasma samples were collected on Days -1 and 6 immediately before lunch (predose) and

at 15, 25, 40, 60, 80, 100, 120, 140, 160, 180, 210, 240, 270, and 300 min after intake of the first portion of orange juice (i.e. ~1/3 of the ethanol dose) at lunch.

Orlistat: Plasma samples were collected on Day 1 immediately before breakfast (predose) and on Days 3, 5, and 6 two hours after dosing, mid-way through lunch.

Fecal fat collection: Days -5 to 8: daily feces until discharge.

#### ASSAY:

Orlistat:

Ethanol:

#### DATA ANALYSIS:

Analysis of covariance of ethanol pharmacokinetic parameters determined by model independent methods and 90% confidence intervals for parameters.

Statistical Summary of the Pharmacokinetic Parameters of Ethanol Prior to (Day -1) and During (Day 6) Treatment with 120 mg Orlistat (B) or Placebo (A) tid for Six Days (N=10)

Parameter	Day -1*		Day 6*		Day 6 B/A	Day 6 90% CI
	B	A	B	A		
$t_{max}$ (min)	37.0	46.0	39.1	33.9	5.23 <sup>b</sup>	-7.9, 18.3
$C_{max}$ (g/L)	0.42	0.41	0.43	0.43	1.01	0.89, 1.15
$AUC_{0-1}$ (g•min/L)	54.6	53.2	51.0	51.9	0.98	0.88, 1.09
$AUC_{0-∞}$ (g•min/L)	67.7	63.0	60.9	64.1	0.95	0.84, 1.07
$\lambda_z$ (min <sup>-1</sup> )	0.0105	0.0134	0.0146	0.0116	0.0030 <sup>b</sup>	-0.0002, 0.0061
$t_{1/2}$ (min)*	66.2	52.0	50.1	56.0		

\*Harmonic mean.

<sup>a</sup> = Geometric least-squares mean.

<sup>b</sup> = Difference between least-squares mean (Group B - Group A).

#### CONCLUSION/LABELING CLAIM:

Inhibition of dietary fat absorption during short-term treatment (six days) with orlistat was not altered by the concomitant ingestion of social amounts of ethanol. Moderate alcohol intake had no influence on orlistat blood levels. Short-term treatment with orlistat had no significant influence on ethanol pharmacokinetics.

#### REVIEWER COMMENTS

1) Ethanol assay sufficiently validated.

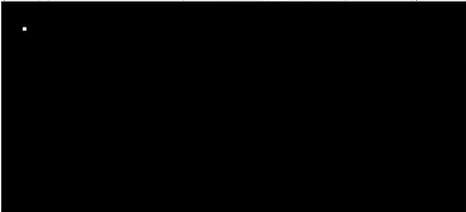
Appendix 1.5.3.2. The Effect of Orlistat (Ro 18-0647) on the  
Pharmacokinetics of Glyburide in Healthy Volunteers (Protocol N3671B)

VOLUME: 1.148

OBJECTIVES:

To assess the influence of orlistat (Ro 18-0647) on the pharmacokinetics of glyburide.

INVESTIGATOR/SITE:



FORMULATIONS:

Glyburide: (Micronase®, Upjohn) 5-mg tablets, lot no. 659 FM

Orlistat: 80-mg capsules (Ro 18-0647/050, batch no. GMZ 749 C01, clinical order no. C162920-05)

Orlistat Placebo: matching capsules (Ro 18-0647/054, batch no. GMZ 754 B01, clinical order no. C162770-20)

STUDY METHODS:

(a) Design: Open-label, placebo-controlled, randomized, two-way crossover with a five-day washout period between two treatments; each subject received single 5 mg doses of glyburide administered orally on the fifth day of orlistat placebo (tid for 4 1/3 days) and orlistat (80 mg tid for 4 1/3 days).

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
12/0	22-38	58.7-77.7	4 White
			4 Black
			3 Hispanic
			1 Mulatto

(c) Sampling times:

Days 5 and 10: blood and plasma samples were collected at 0 h (predose); and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 12, 16, and 24 h postdose of glyburide

ASSAY:

Plasma glyburide concentration was determined by [REDACTED] detection.

Blood glucose was measured with the [REDACTED]

DATA ANALYSIS:

Model independent methods followed by the standard ANOVA for crossover designs and 90% confidence intervals for parameters.

## RESULTS

Comparison of the Mean Pharmacokinetic Parameters (Excluding Subject No. 1) Between the Glyburide Regimens With Placebo and Orlistat Pretreatment

Parameter	Treatment A	Treatment B	90% CI*	
	Placebo p.o. t.i.d. (n=11)	Orlistat p.o. 80 mg t.i.d. (n=11)	Treatment B/A (n=11)	for Treatment B/A
$C_{max}$ (ng/mL)	131 <sup>†</sup>	138 <sup>†</sup>	1.06	(0.91 - 1.23)
$t_{max}$ (h)	3.0	3.7	0.7 <sup>b</sup>	(-0.2 - 1.7 <sup>b</sup> )
$AUC_{0-t}$ (ng·h/mL)	715 <sup>†</sup>	727 <sup>†</sup>	1.02	(0.80 - 1.29)
AUC (ng·h/mL)	1095 <sup>**</sup>	974 <sup>**</sup>	0.89 <sup>a</sup>	(0.66 - 1.21)
$\lambda_2$ (h <sup>-1</sup> )	0.216 <sup>a</sup>	0.188 <sup>a</sup>		
$t_{1/2}$ (h)	3.2 <sup>**</sup>	3.7 <sup>**</sup>		

<sup>a</sup> n=5. <sup>b</sup> for Treatment B - A. CI = Confidence Interval. <sup>†</sup> Geometric least squares mean. <sup>\*\*</sup> Harmonic mean.

## CONCLUSION:

Orlistat does not significantly alter the pharmacokinetics and blood-glucose lowering effect induced by a single oral dose of glyburide in healthy volunteers.

## REVIEWERS COMMENTS:

- 1) Do not agree with dropping Subject 1. Subject 2 has nearly as high levels as Subject 1. With such a variable compound, would expect occasional results like this. The confidence intervals shown in the main text of the review should be considered correct.
- 2) Overall, study is inconclusive due to small sample size and lack of power. However, examining the individual graphs, it does not appear that a systematic effect of orlistat on glyburide is seen.
- 3) Only 80 mg orlistat given in this study.

APPEARS THIS WAY ON ORIGINAL

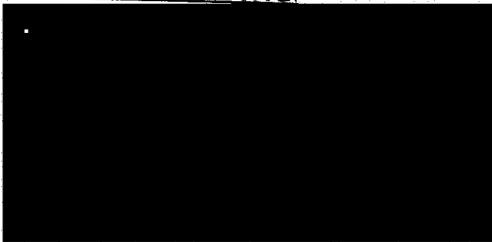
Appendix 1.5.3.3. The Effect of Xenical™ (Orlistat) on the Pharmacokinetics of Nifedipine Extended Release Tablets (Procardia XL®) in Healthy Volunteers  
(Protocol NK14856B)

VOLUME: 1.147

OBJECTIVES:

To assess the effect of Xenical™ (orlistat) on the pharmacokinetics of nifedipine extended release tablets (Procardia XL®) in healthy volunteers.

INVESTIGATOR/SITE:



FORMULATIONS:

Procardia: Procardia XL® (Pfizer Pratt Pharmaceuticals) 60-mg tablets, lot No. 47P108E  
Orlistat: 120-mg capsules (Ro 18-0647/090 batch no. PT2157 T27, clinical order no. C174493-003)  
Orlistat Placebo: matching capsules (Ro 18-0647/098, batch no. PT2160 T32, clinical order no. C176803-004)

STUDY METHODS:

(a) Design: Third-party blind, placebo-controlled, randomized, two-way crossover with at least a one-week washout (for nifedipine) period between treatments. A single oral dose of 60 mg nifedipine GITS was administered on two separate occasions: on the fourth day of orlistat 120 mg and placebo tid for 6 days.

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
15/2	22 - 45	64.3 - 89.6	7 White
			8 Black
			2 Hispanic

(c) Sampling times:

Day 4: plasma samples were collected at 0 h (predose); and 2, 4, 8, 12, 24, 36, 48, and 72 h postdose of nifedipine

ASSAY:

Plasma concentrations of nifedipine were assayed by a [redacted] with [redacted] method.

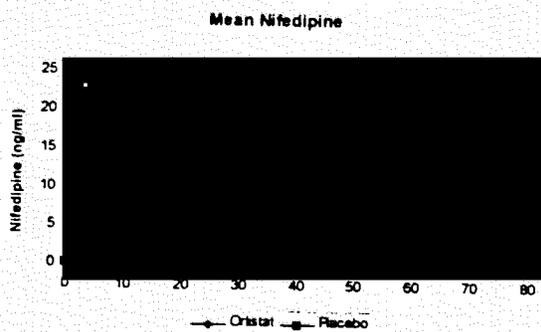
DATA ANALYSIS:

Model independent methods followed by the standard ANOVA for crossover designs and 90% confidence intervals for parameters.

Results

Summary of Statistical Results (n=17) for the Absorption Parameters of Nifedipine Administered with Orlistat (A) or with Placebo (B). Values in the table are least-squares means

Parameter	Treatment A: Orlistat	Treatment B: Placebo	Mean Ratio (90% CI)
C <sub>max</sub>	24.7	23.1	1.07 (0.87, 1.32)
AUC(0-t)	653.3	588.9	1.11 (0.85, 1.44)



**BEST POSSIBLE**

CONCLUSION/LABELING CLAIM:

Therapeutic doses of orlistat 120 mg tid do not significantly alter the pharmacokinetics of a single 60-mg dose of nifedipine GITS in healthy volunteers.

REVIEWER COMMENTS

- 1) Agree with conclusions, although do not agree with dropping Subject 2 as an outlier. The data above use Subject #2.
- 2) Study is not powered to conclusively show that orlistat has not effect, but examining the individual plots, there seems to be no sytematic effect of orlistat.

Appendix 1.5.3.4. Open, Parallel Group Interaction Study of Ro 18-0647 on the Pharmacokinetics and Pharmacodynamics of Pravastatin in Hospitalized Healthy Volunteers (BK14001A)

VOLUME: 1.136

OBJECTIVES:

To investigate the influence of Ro 18-0647 on the pharmacokinetics of pravastatin and on the pharmacodynamic response to pravastatin.

INVESTIGATOR/SITE:



FORMULATIONS:

Pravastatin: tablet containing 20 mg pravastatin (Selektine®, Batch no. 91J14154).  
Orlistat: 120 mg capsule (Ro 18-0647/090, batch no. PT 2157 T02).

STUDY METHODS:

(a) Design: Open-label, randomized, parallel group study in which mildly hypercholesterolemic male volunteers received 40 mg pravastatin qd on days 1-10 (group A) or 40 mg pravastatin qd on days 1-10 and 120 mg Ro 18-0647 tid on days 2-10 (group B).

(b) Demographics:

Gender (M/F)	Age (yr)	Weight (kg)	Origin
24/0	19-40	68.9-97.4	24 White

(c) Sampling times:

Pravastatin: Days 1 and 10: plasma samples were collected at 0 h (predose); and 0.5, 1, 1.5, 2, 3, 4, 6, 8, 10, and 12 h postdose of pravastatin Days 3, 5, 7, and 9: 1 h postdose of pravastatin

Orlistat: Days 2 and 10 (Group B only): plasma samples were collected at 2 h post- morning dose of Ro 18-0647

ASSAY:

Plasma Ro 18-0647 and pravastatin were determined by

Serum total cholesterol, HDL cholesterol, and triglycerides were performed according to standard procedures.

DATA ANALYSIS:

Model independent methods followed by an ANOVA with factor group separately for day 1 and day 10 (this is equivalent to an unpaired t-test). Because of large inter-subject variability, an additional exploratory analysis was performed for the intra-subject differences of AUC between day 1 and day 10 (paired t-test within groups A and B).

## RESULTS

Mean (CV) Pharmacokinetic Parameters of Pravastatin Following Multiple Dose Administration of 40 mg Pravastatin Once Daily (Group A) or of 40 mg Pravastatin Once Daily and 120 mg Ro 18-0647 tid (Group B)

	Group A		Group B	
	Day 1	Day 10	Day 1 <sup>a</sup>	Day 10
t <sub>max</sub> (h)	0.96 (47)	1.3 (32)	1.3 (26)	1.2 (21)
C <sub>max</sub> (ng/mL)	38.5 (66)	35.4 (82)	34.8 (38)	43.9 (46)
AUC <sub>0-∞</sub> (ng•h/mL)	68.3 (62)	68.3 (65)	66.9 (39)	89.2 (41)
t <sub>1/2</sub> (h)	1.9 (43)	1.9 (32)	1.7 (33)	2.1 (17)

Mean Percentage Changes between Day -1 (Baseline) and Day 10, Difference of Mean and the Corresponding 95% Confidence Intervals (CI) of Plasma Lipid Parameters

Parameter	Group A		Group B		Difference of Mean (B - A)	CI
	Mean %	SD	Mean %	SD		
HDL-cholesterol	-5.79	14.4	-5.23	12.6	0.56	± 11.4
LDL-cholesterol	-33.0	7.52	-44.0	9.80	-11.0	± 7.4
Total Cholesterol	-27.2	5.40	-35.1	8.28	-7.9	± 5.9
Triglycerides	-21.7	22.8	-25.6	16.8	-3.9	± 17.0

## CONCLUSION/LABELING CLAIM:

Although no statistical difference was found between the day 10 pravastatin AUCs of the two treatment groups (with and without orlistat), co-administration of Ro 18-0647 for 10 days tended to increase the bioavailability of pravastatin (~35%). On the other hand, it appears that the effect of orlistat on the lipid-lowering action of pravastatin was additive to that of pravastatin alone.

## REVIEWER COMMENTS:

- 1) Some enhancement of absorption, and an increase in the hypolipidemic effect, most likely due to the decreased fat absorption seen.
- 2) As in other studies, only spradic amount of orlistat detected.

APPEARS THIS WAY ON ORIGINAL

Appendix 1.5.4. Fat-Soluble Vitamins And Their Analogues

Appendix 1.5.4.1. The Effect of Orlistat (Ro 18-0647) on the Absorption of Vitamins A and E In Healthy Volunteers  
(Protocol NK14277A)

VOLUME: 1.141 - 1.142

OBJECTIVES:

To assess the effect of orlistat (Ro 18-0647) on the absorption of vitamins A and E.

INVESTIGATOR/SITE:



FORMULATIONS:

- Vitamin A: 25,000 IU (7500 RE) retinol acetate tablets (Ro 01-5275, clinical order no. C176733-001)
- Vitamin E: 200 IU  $\alpha$ -tocopherol acetate tablets (Ro 01-4213, clinical order no. C176723-001)
- Orlistat: 120-mg capsules (Ro 18-0647/090, batch no. PT2157 T11, clinical order no. C172892-001)
- Orlistat Placebo: matching capsules (Ro 18-0647/098, batch no. PT2160 T26, clinical order no. C173522-001).

**BEST POSSIBLE**

STUDY METHODS:

- (a) Design: Open-label, placebo-controlled, randomized, two-way crossover with at least a two-week washout (for vitamin A) period between treatments. Each subject received a single oral dose of 25,000 IU (7500 RE) vitamin A (one 25,000 IU tablet) 24 h before a single oral dose of 400 IU vitamin E (two 200 IU tablets), on two occasions, during treatment with orlistat 120 mg or matching placebo tid for 9 days.

- (b) Demographics:
- | Gender (M/F) | Age (yr) | Weight (kg) | Origin      |
|--------------|----------|-------------|-------------|
| 12/0         |          | 20 - 44     | 65.7 - 94.5 |
|              |          |             | 6 White     |
|              |          |             | 5 Black     |
|              |          |             | 1 Hispanic  |

- (c) Sampling times:

Vitamin A: serum samples were collected at 0 h (predose); and 2, 3, 4, 5, 6, 7, 8, 10, 12, and 24 h postdose of vitamin A.

Vitamin E and cholesterol and triglycerides: serum samples were collected at 0 h (predose); and 4, 8, 12, 24, 36, 48, 72, 96, and 120 h postdose of vitamin E.

ASSAY:

Serum retinol:  
Serum  $\alpha$ -Tocopherol:



DATA ANALYSIS:

Model independent methods followed by the standard ANOVA for crossover designs and 90% confidence intervals for parameters. Vitamin E was analyzed using the ratio of  $\alpha$ -tocopherol to the sum of total cholesterol and triglycerides; also, the vitamin E data was baseline-adjusted before analysis.

Results

Summary of Statistical Results (n=12) of the Pharmacokinetic Parameters of Retinol After Administration of Vitamin A with Orlistat (A) or Placebo (B)

Parameter	A	B	A/B	90% for A/B
$C_0$ ( $\mu\text{g/L}$ )	494*	493*	1.00	0.92, 1.09
$C_{max}$ ( $\mu\text{g/L}$ )	554*	562*	0.99	0.90, 1.08
$t_{max}$ (h)	5.4	4.9	0.50†	-0.74, 1.74†
$AUC_{0-24}$ ( $\mu\text{g}\cdot\text{h/L}$ )	12054*	12289*	0.98	0.90, 1.07

\*Geometric least-squares mean.

†Treatment A - treatment B.

CI = confidence interval.

Summary of Statistical Results (n=12) of the Pharmacokinetic Parameters of Lipid-Adjusted  $\alpha$ -Tocopherol after Administration of Vitamin E with Orlistat (A) or with Placebo (B)

Parameter	A	B	A/B	90% CI for A/B
$C_0$ (mg/10 mg)	0.0297*	0.0300*	0.99	0.97, 1.01
Net $C_{max}$ (mg/10 mg)	0.0140*	0.0245*	0.57	0.44, 0.75
$t_{max}$ (h)	12.7	13.3	-0.67†	-5.27, 3.93†
Net $AUC_{0-120}$ (mg·h/10 mg)	0.4641*	1.1505*	0.40	0.28, 0.59

CONCLUSION/LABELING CLAIM:

Orlistat significantly reduces the absorption of vitamin E (~43% by  $C_{max}$  and ~60% by AUC), but not that of vitamin A.

REVIEWER COMMENTS

- 1) The vitamin A dose given was not large enough to raise levels significantly above baseline. Therefore, no conclusion can be made that orlistat has no effect on absorption. In fact, in view of the effect on beta carotene, it seems likely that there probably is an effect.
- 2) Assay for both A and E sufficiently validated.

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Appendix 1.5.4.2. The Effect Of Orlistat (Ro 18-0647) On The Absorption of  $\beta$ -Carotene in Healthy Volunteers (Protocol NK14179B)

VOLUME: 1.139

OBJECTIVES:

To assess the effect of orlistat (Ro 18-0647) on the absorption of  $\beta$ -carotene and then to examine the effect of  $\beta$ -carotene dose on the extent of inhibition of its absorption due to orlistat treatment.

INVESTIGATOR/SITE:



FORMULATIONS:

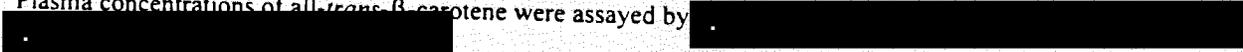
- $\beta$ -Carotene: (Solatene®, Roche Laboratories) 10% beadlet capsules containing 30 mg  $\beta$ -carotene (C159289-001)  
 $\beta$ -Carotene Placebo: matching capsules (C159299-001)  
Orlistat: 120-mg capsules (Ro 18-0647/090, batch no. PT2157 T19, clinical order no. C173292-001)  
Orlistat Placebo: matching capsules (Ro 18-0647/098, batch no. PT2160 T06, clinical order no. C169121-005).

STUDY METHODS:

- (a) Design: Open-label, parallel, placebo-controlled, randomized, two-way crossover with a five-week washout (for  $\beta$ -carotene) period between treatments. A single oral dose of 0, 30, 60, or 120 mg  $\beta$ -carotene was administered on two occasions: on the fourth day of orlistat 120 mg and matching placebo tid for 6 days.
- (b) Demographics:
- | Gender (M/F) | Age (yr) | Weight (kg) | Origin  |
|--------------|----------|-------------|---|
| 47/1         | 19-58    | 57.7- 98.6  | 18 White<br>24 Black<br>5 Hispanic<br>1 Other |
- (c) Sampling times:  
Study Days 4 and 39: serum samples were collected at 0 h (predose); and 4, 8, 12, 24, 36, 48, 72, 96, 168, 240, 336, and 432 h postdose of  $\beta$ -carotene

ASSAY:

Plasma concentrations of all-trans  $\beta$ -carotene were assayed by



DATA ANALYSIS:

Model independent methods followed by the standard ANOVA for crossover designs and 90% confidence intervals for parameters.  $\beta$ -Carotene data were baseline-adjusted before analysis.

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## RESULTS

Summary of Pharmacokinetic Parameters of  $\beta$ -Carotene (n=12). Values in the table are baseline-corrected.

Parameter	30 mg $\beta$ -carotene		60 mg $\beta$ -carotene		120 mg $\beta$ -carotene	
	Orlistat	Placebo	Orlistat	Placebo	Orlistat	Placebo
Net Cmax ( $\mu\text{g/L}$ )	96.1	162.7	189.9	264.4	218.9	340.2
Net Cmax Ratio	0.59 (0.32, 1.09)		0.72 (0.54, 0.96)		0.64 (0.44, 0.93)	
Net AUC ( $\mu\text{g} \cdot \text{h/L}$ )	4817	7248	9626	13655	12106	19657
Net AUC Ratio	0.66 (0.30, 1.47)		0.70 (0.51, 0.98)		0.62 (0.42, 0.90)	

### CONCLUSION/LABELING CLAIM:

Short-term treatment (three to six days) with orlistat did not alter endogenous  $\beta$ -carotene profiles in plasma. When  $\beta$ -carotene was given during orlistat treatment, orlistat reduced the absorption of  $\beta$ -carotene by approximately one-third. This reduction was consistent at all three active dose levels of  $\beta$ -carotene studied.

### REVIEWER COMMENTS

- 1) Only all-trans measured, but interconversion occurs readily in vivo.
- 2) Capacity-limited absorption of  $\beta$ -carotene is well-known.
- 3) A 30 mg supplement still increases  $\beta$ -carotene levels over baseline even with orlistat, and should be adequate for supplementation.

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# SYNOPSIS OF RESEARCH REPORT W-144991 (PROTOCOL BD14419)

COMPANY: F. Hoffmann-La Roche Ltd. NAME OF FINISHED PRODUCT: ORLISTAT NAME OF ACTIVE INGREDIENT: THL	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 BD14419: Effect of orlistat (Xenical™) or placebo treatment on pre- and post- heparin lipoprotein lipase (LPL) and hepatic lipase (HPL) activity following a fat-rich breakfast. Research Report W-144991 / 30 August 1996.																
INVESTIGATOR(S) / CENTER(S)																	
PUBLICATION	None																
PERIOD OF TRIAL	21 September 1995 - 26 March 1996	CLINICAL PHASE I															
OBJECTIVES	<ol style="list-style-type: none"> <li>1. To estimate the effect that orlistat has on post-heparin HPL activity as compared to placebo at 8 h after treatment on day 10</li> <li>2. To descriptively compare the two treatments using activity measures of pre- and post-heparin lipase, as well as a lipid profile to characterize:           <ul style="list-style-type: none"> <li>• pre-heparin LPL specific activity and HPL activity on day 5</li> <li>• post-prandial plasma profiles of TG, VLDL, HDL, LDL and FFA on day 5.</li> <li>• post-heparin LPL activity on day 10.</li> </ul> </li> </ol>																
METHODOLOGY	Single centre, double-blind, randomized, parallel group, placebo-controlled study.																
NUMBER OF SUBJECTS	N = 24, randomised = 24, withdrawn = 0																
DEMOGRAPHIC DATA	<table border="1"> <thead> <tr> <th></th> <th>orlistat</th> <th>Placebo</th> </tr> </thead> <tbody> <tr> <td>N</td> <td>12</td> <td>12</td> </tr> <tr> <td>Sex (M/F)</td> <td>12/0</td> <td>12/0</td> </tr> <tr> <td>Age (yr) - mean ± SD</td> <td>34.6 ± 7.7</td> <td>31.3 ± 8.6</td> </tr> <tr> <td>min - max</td> <td>24 - 47</td> <td>22 - 55</td> </tr> </tbody> </table>			orlistat	Placebo	N	12	12	Sex (M/F)	12/0	12/0	Age (yr) - mean ± SD	34.6 ± 7.7	31.3 ± 8.6	min - max	24 - 47	22 - 55
	orlistat	Placebo															
N	12	12															
Sex (M/F)	12/0	12/0															
Age (yr) - mean ± SD	34.6 ± 7.7	31.3 ± 8.6															
min - max	24 - 47	22 - 55															
DIAGNOSIS AND MAIN CRITERIA FOR INCLUSION	Healthy male volunteers.																
TRIAL DRUG / STROKE (BATCH) NOs DOSE / ROUTE / REGIMEN / DURATION	orlistat 120 mg capsule (Ro 18-0647/008, C176983) 120 mg p.o. t.i.d. on days 1-4 120 mg p.o. b.i.d. on day 5 (at breakfast and dinner) 120 mg p.o. t.i.d. on days 6-9 120 mg p.o. on day 10 (at breakfast)																

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## SYNOPSIS OF RESEARCH REPORT W-144991 (PROTOCOL BD14419) continued

REFERENCE DRUG / STROKE (BATCH) NOS DOSE / ROUTE / REGIMEN / DURATION	Placebo capsule (Ro 18-0647/008, C175063) 1 capsule p.o. t.i.d. on days 1-4 1 capsule p.o. b.i.d. on day 5 (at breakfast and dinner) 1 capsule p.o. t.i.d. on days 6-9 1 capsule on day 10 (at breakfast)
CRITERIA FOR EVALUATION EFFICACY:	NA - Healthy volunteer study.
SAFETY:	Physical examination, vital signs, electrocardiogram, adverse events, laboratory tests.
PHARMACODYNAMICS:	Post-heparin HPL activity, specific LPL and HPL activity, TG, VLDL, HDL, LDL and FFA concentrations.
PHARMACOKINETICS:	Plasma concentrations of orlistat and M1, M3 metabolites.
STATISTICAL METHODS	Descriptive statistics.

### PROCEDURE:

This was a double-blind, randomised, parallel group, placebo-controlled study in two groups of healthy male subjects. Two groups of 12 subjects received orlistat 120 mg or placebo t.i.d. during meals on days 1-4, and on the morning of day 5 during a fat-rich breakfast. Plasma pre-heparin LPL activity and mass, HPL activity, TG, VLDL, HDL, LDL and FFA were monitored hourly during a 12 h postprandial period. Orlistat or placebo treatment resumed with dinner on day 5, and continued t.i.d. on days 6-9. On the morning of day 10, the subjects received orlistat or placebo during a fat-rich breakfast. Intravenous heparin sodium (100 IU/kg) was administered 7½ h after treatment, and 8 h after treatment post-heparin LPL activity and mass and HPL activity was measured.

In addition to the blood samples taken for pharmacodynamic evaluation, samples were taken for pharmacokinetic analysis on day 1 before breakfast, on day 5 before breakfast and 2, 4, 6, 8, 10 and 12 h after treatment, and on day 10 before breakfast, immediately before the heparin injection, and immediately prior to the post-heparin LPL and HPL blood samples.

### PHARMACOKINETIC RESULTS:

Detectable orlistat plasma levels (0.2 - 3.37 ng/mL) were most frequent at 2 to 6 hours after the morning dose on day 5. Concentrations of the metabolites M1 and M3 were found in almost all plasma samples after treatment. The average half lives of M1 and M3 were approximately 3 and 13 hours respectively.

### PHARMACODYNAMIC RESULTS:

Primary measure: There was no significant difference between the treatment groups (placebo-orlistat) for post-heparin HPL activity; mean and 90% CI for the difference: -956.9 [-7523.1, 5609.3]. This result is further substantiated by the mean and 90% CI for the ratio (orlistat/placebo) of post-heparin HPL: 1.07 [0.87, 1.27]. The intersubject coefficient of variation for post-heparin HPL activity was 29.7%. This value was higher than that estimated from the literature as 19%.

Secondary Measures: No significant treatment differences were apparent in any of the secondary measures.

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SYNOPSIS OF RESEARCH REPORT W-144991 (PROTOCOL BD14419) continued

SAFETY RESULTS:

The drug was well tolerated. Fourteen of the 24 subjects reported a total of 23 adverse events. 12 on orlistat. 2 on placebo. All of the adverse events were associated with the lower gastrointestinal tract and included loose stools, oily spotting and flatus. Most (21/23) of the events were assessed as mild in intensity, and as probably related to treatment in 11 of the subjects receiving orlistat. No treatment was given for any adverse event reported. There were no treatment related effects on vital signs or laboratory parameters. There were no deaths, serious adverse events or adverse events leading to premature withdrawal from the study.

CONCLUSIONS:

Orlistat and its metabolites had no apparent effect on systemic fasting and post-prandial pre- and post-heparin HPL and LPL activity. No treatment-related alteration in lipoprotein metabolism was detected. Orlistat was well tolerated.

Reviewer's Comments: LC/MS/MS assays for orlistat and M1 sufficiently validated. LC/MS/MS assay for M3 less extensively validated due to low purity of M3 standard. (RMS)

Summary of orlistat plasma concentrations (Day 5) from BD14419

Time (h)	Conc (ng/mL)	
	N*	Range
Pre-dose	0	-
2	7	0.2 - 3.37
4	8	0.27 - 2.07
6	4	0.32 - 0.54
8	0	-
10	0	-
12	0	-

\* Number of samples (Total=12) that contain measurable concentrations of orlistat

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