

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

21-853

21-654s016

**CLINICAL PHARMACOLOGY AND
BIOPHARMACEUTICS REVIEW(S)**

CLINICAL PHARMACOLOGY REVIEW

NDA: 21-853	Submission Date(s): December 11, 2006
Brand Name	Omacor®
Generic Name	omega-3-acid ethyl esters
Reviewer	Sally Y. Choe, Ph.D.
Team Leader	S. W. Johnny Lau, Ph.D. (Acting)
OCP Division	Clinical Pharmacology II
OND Division	Metabolism and Endocrinology Products (HFD-510)
Sponsor	Reliant Pharmaceuticals, Inc.
Relevant NDA(s)	21-654
Submission Type; Code	NDA Resubmission
Formulation; Strength(s)	1 mg strength capsule
Indication	Combination therapy with HMG-CoA reductase inhibitors for hypertriglyceridemia

1.	EXECUTIVE SUMMARY	2
1.1	RECOMMENDATION	2
1.2	PHASE IV COMMITMENTS.....	2
1.3	SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS.....	2
2.	DETAILED LABELING RECOMMENDATIONS.....	4
3.	APPENDICES.....	18
3.1	INDIVIDUAL STUDY REVIEWS: OMA-104.....	18
3.2	ANALYTICAL METHOD VALIDATION.....	25

1. EXECUTIVE SUMMARY

1.1 RECOMMENDATION

One of the deficiencies identified in the Agency's approvable letters dated 11/10/2004 for NDA 21-853 is the insufficient data to ensure that co-administration of Omacor with LDL-lowering drugs, such as HMG-CoA reductase inhibitors (statins), will not attenuate the clinical effectiveness of the statin due to any pharmacokinetic interactions. This submission has addressed this deficiency adequately from a Clinical Pharmacology perspective provided that a mutually satisfactory agreement is reached between the Agency and the Sponsor regarding the language in the labeling

1.2 PHASE IV COMMITMENTS

None

1.3 SUMMARY OF CLINICAL PHARMACOLOGY FINDINGS

Omacor® (omega-3-acid ethyl esters), a lipid-regulating agent, contains the ethyl esters of omega-3 fatty acids, principally eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). Since EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis and inhibit esterification of other fatty acids, Omacor® may reduce the synthesis of triglycerides. Omacor® has been approved under NDA 21-654 for the treatment of patients with triglycerides \geq 500 mg/dL. The recommended daily dosage is 4 g, which may be taken in a single dose or in 2 divided doses.

Under NDA 21-853, Omacor® has received an approvable letter for the indication in combination with statin therapy for the treatment of patients with blood triglycerides between 200 and 500 mg/dL. One of the deficiencies that has been identified was that insufficient data were provided to ensure that co-administration of Omacor® with LDL lowering drugs, such as HMG-CoA reductase inhibitors (statins), will not attenuate the clinical effectiveness of the statin either due to the pharmacodynamic effect or in relation to any pharmacokinetic interactions. The applicant submitted two clinical study reports in response to the approvable letter; a drug-drug interaction study with simvastatin and a combined Omacor® and simvastatin therapy Phase 3 study. The Office of Clinical Pharmacology focused its review on the drug interaction study. The complete Clinical Pharmacology review on Omacor® from the original NDA 21-853 and NDA 21-654 submissions were conducted by Dr. Wei Qiu dated 10/20/2004.

The final clinical study report submitted is entitled "A Pharmacokinetic Interaction Study Evaluating the Effect of Reliant Pharmaceuticals Inc. (Omacor®) Omega-3-Acid Ethyl Esters Capsules on the Plasma Pharmacokinetics of Merck & Co. (Zocor®) Simvastatin Tablets in Healthy Adult Volunteers Under Fasting Conditions." This study shows that while the AUCs of simvastatin and β -hydroxy simvastatin increased by approximately 25% and 10-19%, respectively when Zocor® was coadministered with Omacor® versus when administered alone, Omacor® does not appear to affect the pharmacokinetics of Zocor® following repeated-dose administration. The following table shows the summary of the relative bioavailability results from Day 1 and Day 14 for both simvastatin and β -hydroxy simvastatin.

Table 11.4.2:1 Relative Bioavailability Assessment – Ratios of LSM and 90% CI

Parameter Day 1	Simvastatin	β -Hydroxy Simvastatin
	A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h versus B: Zocor [®] 80 mg, Q24h	A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h versus B: Zocor [®] 80 mg, Q24h
AUC _{0-t}	124.9% (100.5 – 155.2%)	110.2% (95.9 – 126.6%)
AUC _{inf}	127.9% (101.6 – 161.0%)	118.9% (101.2 – 139.5%)
C _{max}	114.1% (98.7 – 131.8%)	104.6% (91.3 – 119.9%)
Parameter Day 14		
AUC _{τ}	99.8% (91.5 – 108.8%)	97.5% (82.0 – 116.0%)
C _{max}	110.1% (97.3 – 124.6%)	93.5% (83.3 – 105.0%)

Appears This Way
On Original

14 Page(s) Withheld

 Trade Secret / Confidential (b4)

✓ Draft Labeling (b4)

 Draft Labeling (b5)

 Deliberative Process (b5)

3. APPENDICES

3.1 INDIVIDUAL STUDY REVIEWS: OMA-104

Clinical Study OMA-104

TITLE: A Pharmacokinetic Interaction Study Evaluating the Effect of Reliant Pharmaceuticals Inc. (Omacor®) Omega-3-Acid Ethyl Esters Capsules on the Plasma Pharmacokinetics of Merck & Co. (Zocor®) Simvastatin Tablets in Healthy Adult Volunteers Under Fasting Conditions

INVESTIGATOR: Dennis Swearingen, MD

STUDY CENTER: MDS Pharma Services
4747 East Beautiful Lane
Phoenix, Arizona 85044

PHARMACOKINETIC AND STATISTICAL ANALYSIS:

MDS Pharma Services
2350 Cohen Street, Saint-Laurent,
Montreal, Quebec, Canada, H4R 2N6

BIOANALYTICAL ANALYSIS:

MDS Pharma Services
2350 Cohen Street, Saint-Laurent,
Montreal, Quebec, Canada, H4R 2N6

STUDY PERIOD: March 13 to April 27, 2006

OBJECTIVE: The objective of this study was to determine the impact of Reliant Pharmaceuticals, Inc. (Omacor®), omega-3-acid ethyl esters capsules (4 g dose) on the plasma pharmacokinetics of Merck & Co. (Zocor®) 80 mg simvastatin tablets.

STUDY DESIGN: This is a single center, randomized, open-label, 2-way, crossover drug-drug interaction study evaluating single-dose and steady state kinetics in healthy male and female subjects under fasting conditions. Subjects were housed in the clinical research unit from at least 10 hours before the initial dosing on Day 1 until 24 hours following the last morning dose on Day 14. The washout period was at least 14 days between the last dose of Period 1 and the first dose of Period 2. The following table summarizes the treatments administered.

Study Treatments	Investigational Products	Doses
Treatment A (Test)	Reliant Pharmaceuticals, Inc. (Omacor®) 1 g omega-3-acid ethyl esters capsules and Merck & Co. (Zocor®) 80 mg simvastatin tablets.	Oral 80 mg dose of simvastatin and 4 g dose (4 capsules) of omega-3-acid ethyl esters, administered QD (every 24 hours) with 240 mL of water on the mornings of Days 1 through 14, for a total of 14 doses.
Treatment B (Reference)	Merck & Co. (Zocor®) 80 mg simvastatin tablets.	Oral 80 mg dose of simvastatin, administered QD with 240 mL of water on the mornings of Days 1 through 14, for a total of 14 doses.

BLOOD SAMPLE COLLECTION: 5 mL of blood samples were collected in blood collection tubes containing ethylenediaminetetra-acetic acid (EDTA) before the initial dosing (on Day 1), before the 12th, 13th, and 14th doses (on Days 12, 13, and 14) and at the following times after the first and 14th doses: 0.333, 0.5, 0.75, 1, 1.5, 2, 2.75, 3.5, 4.25, 5, 6, 7.5, 9, 11, 13, 16, 20, and 24 hours.

SAFETY ASSESSMENT: Safety parameters included the occurrence of adverse events and clinical laboratory parameters. The clinical laboratory results included serum chemistry, hematology, urinalysis, vital sign, ECG, physical examination and coagulation.

SUBJECTS: Twenty-four normal healthy, male and female subjects (20 males and 4 females) were randomized and completed the study. Subjects were between the ages of 19 and 47 years (mean + SD = 30 + 8 years) and the 20 subjects were Hispanic and 4 were Caucasian.

ANALYTICAL METHOD: A validated HPLC/MS method was employed for the analysis of simvastatin and β -hydroxy simvastatin in human plasma. Simvastatin and its internal standard, simvastatin- d_3 , and β -hydroxy simvastatin ammonium salt and its internal standard, β -hydroxy simvastatin sodium salt- d_3 , were extracted using a solid phase extraction. For simvastatin, a set of eight non-zero point calibration standards covering the range of 0.311 ng/mL to 41.5 ng/mL and quality control (QC) samples at concentrations of 0.933, 4.16, 16.6, and 33.2 ng/mL were prepared with drug free human plasma. For β -hydroxy simvastatin, a set of eight non-zero point calibration standards covering the range of 0.300 ng/mL to 40.0 ng/mL and quality control (QC) samples at concentrations of 0.900, 4.01, 16.0, and 32.0 ng/mL were prepared with drug free human plasma. Average back-calculated standards for simvastatin and β -hydroxy simvastatin had %CV of 2.4 – 5.2% and 2.2 – 4.3%, respectively. While the range of correlation coefficient for analytical runs for simvastatin and β -hydroxy simvastatin was greater than 0.9918 and 0.9924, respectively, the inter-assay %CV of QC for simvastatin and β -hydroxy simvastatin ranged from 4.3 to 9.9% and 3.4 to 5.5%, respectively. There were 52 repeat samples (25 for simvastatin and 27 for β -hydroxy simvastatin) out of 1880 samples analyzed due to unacceptable internal standard response, loss in processing, or reporting above the accepted range. These repeats did not have significant impact on conclusion of the study.

PHARMACOKINETICS

Statistical Methods: Data from 24 subjects were included in the statistical analysis if the subjects completed at least 1 period of the study.

Statistical and PK analyses were performed. Version 9.1.3 (MIXED procedure, SAS Institute Inc, Cary, NC).

A steady-state analysis was performed on the ln-transformed predose C_{min} concentrations of simvastatin and β -hydroxy simvastatin on Days 12, 13, and 14 using Helmert's contrasts using SAS® Mixed and Means procedures. All PK parameters were analyzed by the analysis of variance (ANOVA) in which treatment, sequence, and period as fixed effects and subject-nested-within sequence as a random effect using the SAS® general linear model (GLM) procedure. The time dependence pharmacokinetic linearity was evaluated by comparing the PK parameter, AUC_{τ} (Day 14, AUC over 24 hr) against AUC_{inf} (Day 1) using an ANOVA on the ln-transformed values.

Results:

The summary of the pharmacokinetic parameters for simvastatin and β -hydroxy simvastatin are given in the following tables.

Table 11.4.1.2:1 Pharmacokinetic Parameters for Simvastatin and β -Hydroxy Simvastatin Following Oral Doses – Geometric Mean (CV%)

Parameter Day 1	Simvastatin		β -Hydroxy Simvastatin	
	Treatment A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	Treatment B: Zocor [®] 80 mg, Q24h	Treatment A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	Treatment B: Zocor [®] 80 mg, Q24h
AUC _{0-t} (ng·h/mL)	102.7 (72.4)	81.7 (79.7)	43.2 (68.7)	38.6 (72.9)
AUC _{inf} (ng·h/mL)	112.2 (69.3)	84.6 (77.0)	53.0 (67.8)	43.9 (77.4)
C _{max} (ng/mL)	17.3 (71.5)	14.7 (64.3)	4.37 (78.0)	4.02 (71.1)
Parameter Day 14				
AUC _τ (ng·h/mL)	109.8 (58.0)	102.7 (54.3)	73.2 (55.9)	73.7 (56.3)
C _{max} (ng/mL)	13.8 (50.2)	12.2 (49.7)	5.15 (64.7)	5.29 (60.5)

Source: Tables 14.2.5.1 through 14.2.5.4

Table 11.4.1.2:2 Pharmacokinetic Parameters for Simvastatin and β -Hydroxy Simvastatin Following Oral Doses – Arithmetic Mean (\pm SD)

Parameter Day 1	Simvastatin		β -Hydroxy Simvastatin	
	Treatment A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	Treatment B: Zocor [®] 80 mg, Q24h	Treatment A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	Treatment B: Zocor [®] 80 mg, Q24h
t _{max} (h)	2.12 (2.64)	1.74 (1.48)	5.84 (2.29)	5.72 (2.87)
t _{1/2} (h)	5.96 (1.38)	5.64 (1.92)	9.00 (3.53)	6.42 (3.03)
CL/F (L/h)	880 (700)	1181 (887)	NC	NC
V _{area} /F (L)	7901 (7292)	8978 (6222)	NC	NC
Parameter Day 14				
t _{max} (h)	2.35 (2.63)	2.58 (1.87)	5.52 (2.32)	5.60 (1.99)
C _{avg,ss} (ng/mL)	5.21 (2.62)	4.86 (2.67)	3.46 (1.76)	3.50 (1.85)
C _{min} (ng/mL)	1.95 (1.61)	1.98 (1.66)	1.83 (1.31)	1.79 (1.26)
t _{1/2} (h)	7.39 (1.62)	9.92 (5.53)	9.49 (5.76)	9.44 (5.86)
Flux ₁ (%)	292 (151)	271 (132)	146 (62.3)	160 (52.4)
Flux ₂ (%)	1135 (1045)	1021 (946)	395 (362)	467 (459)
CL _{ss} /F (L/h)	838 (477)	872 (402)	NC	NC
R (Accumulation)	1.05 (0.488)	1.23 (0.658)	1.46 (0.527)	1.66 (0.818)

Source: Tables 14.2.3.1 through 14.2.3.8

NC = Not Calculated

The following graphs show the mean plasma profiles of simvastatin and β -hydroxy simvastatin at Day 1 and Days 12-14.

Figure 14.4.2 Mean Plasma Simvastatin Concentrations – Day 1 (Linear Plot)

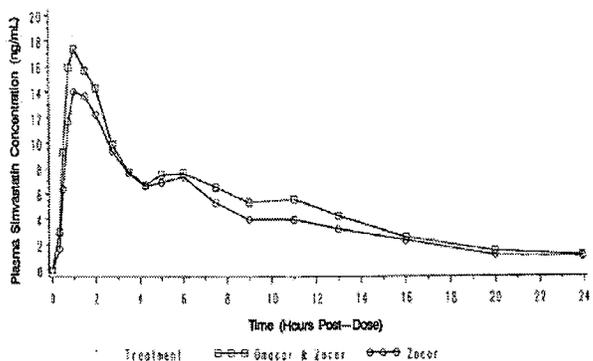


Figure 14.4.4 Mean Plasma Simvastatin Concentrations – Days 12 – 14 (Linear Plot)

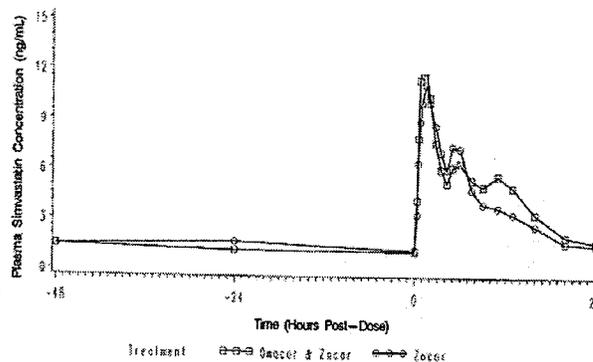


Figure 14.4.8 Mean Plasma β-Hydroxy Simvastatin Concentrations – Day 1 (Linear Plot)

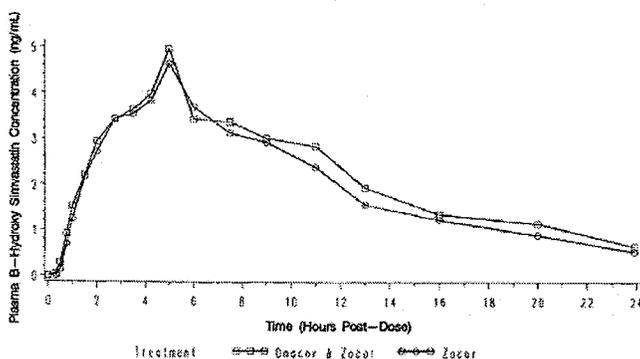
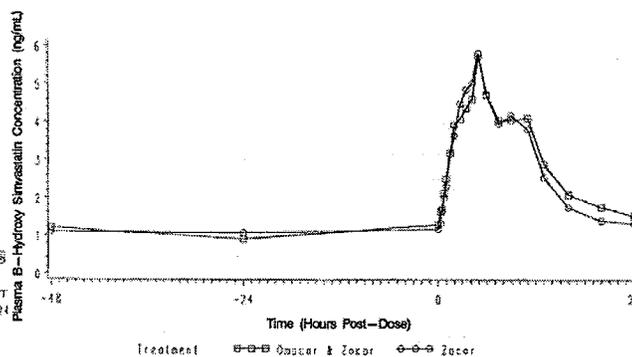


Figure 14.4.10 Mean Plasma β-Hydroxy Simvastatin Concentrations – Days 12 – 14 (Linear Plot)



A summary of the relative bioavailability results from Day 1 and Day 14, the statistical outputs for the steady-state analysis, and the time dependence PK linearity for both simvastatin and β-hydroxy simvastatin are given in the following tables.

Table 11.4.2:1 Relative Bioavailability Assessment – Ratios of LSM and 90% CI

Parameter Day 1	Simvastatin	β-Hydroxy Simvastatin
	A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h versus B: Zocor [®] 80 mg, Q24h	A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h versus B: Zocor [®] 80 mg, Q24h
AUC _{0-t}	124.9% (100.5 – 155.2%)	110.2% (95.9 – 126.6%)
AUC _{inf}	127.9% (101.6 – 161.0%)	118.9% (101.2 – 139.5%)
C _{max}	114.1% (98.7 – 131.8%)	104.6% (91.3 – 119.9%)
Parameter Day 14		
AUC _τ	99.8% (91.5 – 108.8%)	97.5% (82.0 – 116.0%)
C _{max}	110.1% (97.3 – 124.6%)	93.5% (83.3 – 105.0%)

Source: Tables 14.2.5.1 through 14.2.5.4

Table 11.4.2:2 Steady-State Assessment – Cmin Geometric Means for Each Treatment and Time

Analyte	Treatment	Day	Geometric Mean (CV%)
Simvastatin	A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	12	1.0252 (122.4)
		13	0.8449 (121.5)
		14	0.8011 (113.3)
	B: Zocor [®] 80 mg, Q24h	12	0.8483 (166.5)
		13	0.8311 (220.1)
		14	0.7651 (140.8)
β-Hydroxy Simvastatin	A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	12	0.8395 (129.5)
		13	0.6986 (107.1)
		14	0.9062 (117.3)
	B: Zocor [®] 80 mg, Q24h	12	0.7334 (144.0)
		13	0.5887 (197.4)
		14	0.6996 (166.8)

Source: Appendix 16.1.9.6 and 16.1.9.8

Table 11.4.2:3 Steady-State Results – P-values for Helmert's Contrasts

Analyte	Helmert's Contrasts	P-value
Simvastatin	Cmin Day 12 versus mean of (Cmin Day 13 and Cmin Day 14)	0.2275
	Cmin Day 13 versus Cmin Day 14	0.6081
β-Hydroxy Simvastatin	Cmin Day 12 versus mean of (Cmin Day 13 and Cmin Day 14)	0.3118
	Cmin Day 13 versus Cmin Day 14	0.0321

Source: Appendix 16.1.9.6 and 16.1.9.8

Table 11.4.2:4 AUC Geometric Means (CV%) For Each Treatment by Day

Analyte	Treatment	Day	Geometric Mean (CV%)
Simvastatin	A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	1	120.202 (58.3%)
		14	109.835 (58.0%)
	B: Zocor [®] 80 mg, Q24h	1	90.259 (69.2%)
		14	102.749 (54.3%)
β-Hydroxy Simvastatin	A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	1	58.3254 (59.6%)
		14	74.5965 (58.8%)
	B: Zocor [®] 80 mg, Q24h	1	50.8334 (68.4%)
		14	73.6856 (56.3%)

Source: Appendix 16.1.9.9 and 16.1.9.10

Table 11.4.2:5 Time Dependence Pharmacokinetic Linearity – Ratios of LSM (90% CI) for AUC_t/AUC_{inf}

Treatment	Simvastatin	β-Hydroxy Simvastatin
A: Omacor [®] 4 g & Zocor [®] 80 mg, Q24h	88.3% (73.4 - 106.2%)	121.7% (103.6 - 142.9%)
B: Zocor [®] 80 mg, Q24h	108.3% (88.7 - 132.1%)	145.2% (121.9 - 172.8%)

Source: Appendix 16.1.9.9 and 16.1.9.10

Overall, the coadministration of omega-3-acid ethyl esters capsules and simvastatin tablets did not appear to affect the PK of simvastatin at steady state. Following multiple doses for 14 days, the 90% CIs of the ratios of LSM derived from the analyses on the ln-transformed PK parameters AUC_τ and C_{max} were within the 80 - 125% equivalence limits for both simvastatin and β-hydroxy simvastatin.

Following single dose administration, the AUCs of simvastatin increased by approximately 25% when Zocor® was coadministered with Omacor® versus when administered alone.

It seems that steady-state was achieved by Day 12 for simvastatin.

PK linearity was demonstrated for simvastatin with each of the two treatments suggesting no evidence of drug accumulation over the 14-day dosing period. The ratio of LSM was within the 80-125% range for each treatment for both simvastatin and β-hydroxy simvastatin except β-hydroxy simvastatin under Zocor® treatment only.

SAFETY ASSESSMENT: Twenty three out of 24 subjects received all scheduled study doses. Subject 4 received all 14 doses of Treatment A (Omacor® 4 g and Zocor® 80 mg, Q24h) before being discontinued from the study prior to Treatment B (Zocor® 80 mg, Q24h). Subject 4, a 29-year-old Hispanic female experienced the severe SAE of acute cholecystitis during the washout period 4 days after the last scheduled dose of Treatment A. The subject was hospitalized for this SAE, underwent a laparoscopic cholecystectomy, and recovered without sequelae. The Investigator considered the cholecystitis to be unlikely related to study drug. Fourteen of the 24 subjects reported 32 treatment-emergent AEs. Excluding the severe AE of cholecystitis, all AEs were mild. Similar number of subjects reported the AEs after each treatment (9 for Treatment A and 8 for Treatment B). No clinically relevant trends were noted in the serum chemistry, hematology, urinalysis, vital sign, ECG, physical examination, and coagulation findings. Overall, the tolerability of the study drug products was acceptable.

SPONSOR'S CONCLUSIONS:

- At steady state, the extent (AUC_τ) and rate (C_{max}) of exposure to simvastatin and β-hydroxy simvastatin following daily coadministration of Omacor® (4 g) with Zocor® (80 mg) were similar to those following the administration of Zocor® (80 mg) alone. Therefore, Omacor® did not appear to affect the pharmacokinetics of Zocor® following repeated-dose administration.
- Based on the ratios of LSM after single-dose administration, the rate (C_{max}) of exposure to simvastatin and β-hydroxy simvastatin following daily coadministration of Omacor® (4 g) with Zocor® (80 mg) was similar to that following administration of Zocor® (80 mg) alone. Under single-dose conditions only, the AUC of simvastatin, but not the β-hydroxy metabolite, appeared to increase by about 25% when the 2 agents were administered concomitantly.
- Linear pharmacokinetics were demonstrated for simvastatin following repeated-dose administrations of both Zocor® alone, and Zocor® plus Omacor®. Linear pharmacokinetics were demonstrated for β-hydroxy simvastatin with Treatment A (Omacor® 4 g & Zocor® 80 mg, Q24h), but not with Treatment B (Zocor® alone).
- Coadministration of once-daily oral doses of Omacor® (4 g) with Zocor® (80 mg) for 14 consecutive days appeared to be safe and well tolerated by the healthy male and female subjects in this study.

REVIEWER'S COMMENTS:

- The sponsor's conclusion stating that Omacor® did not appear to affect the pharmacokinetics of Zocor® following repeated-dose administration is acceptable.
- Following single dose administration, the AUCs of simvastatin and β -hydroxy simvastatin increased by approximately 25% and 10-19%, respectively when Zocor® was coadministered with Omacor® versus when administered alone.
- The sponsor's explanation behind the demonstration of PK linearity based on the ratios of LSM for AUC_{τ}/AUC_{inf} and their 90% confidence intervals is not acceptable. Although the sponsor claims that the ratios of LSM were within the 80-125% range for simvastatin from each treatment, their 90% confidence intervals were outside of the specified range. It seems that there was a slight accumulation for simvastatin when Zocor® was administered alone whereas the coadministration of Omacor® and Zocor® resulted in reduction in exposure for simvastatin. In both coadministration and Zocor® alone treatments, β -hydroxy simvastatin seems to show some accumulation. These results do not impact the overall conclusion of Omacor® not affecting the pharmacokinetics of Zocor® following repeated-dose administration.

**Appears This Way
On Original**

3.2 ANALYTICAL METHOD VALIDATION

“Validation of a High Performance Liquid Chromatographic Mass Spectrometric Method for the Determination of Simvastatin and β -Hydroxy Simvastatin in Human Plasma (EDTA)” was conducted and an adequately validated HPLC/MS method was established to analyze the human plasma concentration of simvastatin and β -hydroxy simvastatin. The following tables summarize the analytical method validation for simvastatin and β -hydroxy simvastatin:

SIMVASTATIN VALIDATION SUMMARY

Analyte	Simvastatin		
Matrix (Anticoagulant)	Human Plasma (EDTA)		
Preservative	N/AP		
SOP Number	LMS-M-6497-00		
Assay Method	High performance liquid chromatographic mass spectrometric method		
Detector	PE Sciex API III Plus		
Assay Volume Required	500 μ L		
Standard Curve Concentrations	0.311 – 41.5 ng/mL		
Regression Type	Linear (1/concentration ²)		
Quantitation Method	Peak Area Ratio		
Selectivity	No interfering peaks noted in 9 out of 10 blank human plasma samples screened		
Quality Control Samples		Precision (%)	Accuracy (%)
Inter-batch	LLOQ	12.9	-0.6
	Low	8.1	-6.6
	Medium	5.2	-9.0
	High	5.2	-2.1
Intra-batch #2	LLOQ	6.7	0.0
	Low	6.9	-6.2
	Medium	2.1	-9.6
	High	4.7	-1.5
Intra-batch #3	LLOQ	7.8	-12.5
	Low	10.1	-5.9
	Medium	4.5	-4.8
	High	4.4	0.9
Intra-batch #6	LLOQ	10.6	10.9
	Low	8.3	-7.9
	Medium	4.3	-13.3
	High	4.8	-5.7
Recovery		Recovery (%)	
Analyte	Low	68.4	
	Medium	61.2	
	High	60.3	
Long-term Stability	80 days at -20°C 145 days at -80°C		
Short-term Stability	23.5 hours at ambient temperature 22 hours at 5°C		
Freeze and Thaw Stability	5 cycles at -20°C 3 cycles at -80°C		
Post-preparative Stability	132.6 hours at 5°C		
Stock Solution Stability	238 days at 100.0 μ g/mL in acetonitrile at -22°C 32 days at 30.0 ng/mL in acetonitrile at -20°C		
Dilution Integrity	up to 124 ng/mL		
Processed Sample Integrity	103 hours at ambient temperature		

b(4)

Batch Size	83 hours at 5°C
------------	-----------------

β-HYDROXYSIMVASTATIN VALIDATION SUMMARY

Analyte	β-Hydroxysimvastatin		
Matrix (Anticoagulant)	Human Plasma (EDTA)		
Preservative	N/AP		
SOP Number	LMS-M-6497-00		
Assay Method	High performance liquid chromatographic mass spectrometric method		
Detector	PE Sciex API III Plus		
Assay Volume Required	500 µL		
Standard Curve Concentrations	0.300 – 40.0 ng/mL		
Regression Type	Linear (1/concentration ³)		
Quantitation Method	Peak Area Ratio		
Selectivity	No interfering peaks noted in 9 out of 10 blank human plasma samples screened		
Quality Control Samples		Precision (%)	Accuracy (%)
Inter-batch	LLOQ	8.3	3.7
	Low	7.5	-6.3
	Medium	3.1	-7.5
	High	3.3	-6.9
Intra-batch #2	LLOQ	6.5	-4.7
	Low	6.1	-9.0
	Medium	2.3	-7.5
	High	2.6	-7.2
Intra-batch #3	LLOQ	7.5	7.7
	Low	10.7	-4.4
	Medium	2.0	-5.0
	High	3.8	-6.6
Intra-batch #6	LLOQ	5.2	7.3
	Low	4.6	-5.6
	Medium	1.8	-10.0
	High	4.0	-6.9
Recovery		Recovery (%)	
Analyte	Low	84.9	
	Medium	83.2	
	High	87.9	
Long-term Stability	80 days at -20°C 145 days at -80°C		
Short-term Stability	23.5 hours at ambient temperature 22 hours at 5°C		
Freeze and Thaw Stability	5 cycles at -20°C 3 cycles at -80 °C		
Post-preparative Stability	132.6 hours at 5°C		
Stock Solution Stability	587 days at 100.0 µg/mL in 50% acetonitrile in water at -20°C 5 days at 30.0 ng/mL in 50% acetonitrile in water at -20°C		
Dilution Integrity	up to 120 ng/mL		
Processed Sample Integrity	103 hours at ambient temperature 83 hours at 5°C		
Batch Size			

b(4)

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Sally Choe
6/4/2007 11:29:31 AM
BIOPHARMACEUTICS

S.W. Johnny Lau
6/4/2007 05:22:58 PM
BIOPHARMACEUTICS

Study code: CK85-002 cont.

SUMMARY: It was observed that both compounds (TG30 and K85) exerted a significant change in the fatty acid profile. The fraction of EPA increased in a dose-dependent manner in both total lipids and phospholipids. DHA also increased in all subjects, but not dose-dependent. When the same amount of EPA was taken as ethylester or as triglyceride, a similar increase in the fraction of serum EPA was observed. Both formulations exerted a shift in the serum triglyceride fatty acids to a higher degree of unsaturation.
No ethylesters could be detected in the sera from the volunteers taking K85.

CONCLUSIONS: This study shows that omega-3 fatty acids, when taken daily for a two weeks period, are absorbed to the same extent when administered as ethylester or triglyceride.

Appears This Way
On Original

<u>NAME OF COMPANY:</u> Pronova a.s. 13.10.92 <u>NAME OF FINISHED PRODUCT:</u> K85 <u>NAME OF ACTIVE INGREDIENT(S) INN:</u> Icosapent (EPA) ethylester and doconexent (DHA) ethylester.	<u>INDIVIDUAL STUDY TABLE REFERING TO PART OF THE DOSSIER:</u> Volume: Page:	<u>(FOR NATIONAL AUTHORITY USE ONLY)</u>
Study code: CK85-007		
Title of the study: Comparative effects of prolonged intake of highly purified fish oil as ethyl-ester or triglyceride on lipids, hemostasis and platelet function in normolipemic men.		
Investigators: F		
Study centre(s): F		
Publication (reference): Internal report 1992. Abstract presented in Tokyo 1989.		
Study period (years): 1988 Clinical phase: I		
Objectives: To compare the effects of a prolonged daily intake of K85 or TG30 on lipid metabolism and hemostasis in normolipemic men. Corn oil served as control.		
Methodology: The participants were randomly allocated in 3 groups receiving K85, TG30, or corn oil. The trial was double-blind, placebo-controlled regarding the groups allocated to K85 or placebo. The group receiving TG30 was open. Bloodsamples were collected at week 0, 1, 3, and 7.		
Number of subjects (total and for each treatment): 31 subjects divided in 3 groups receiving either 4 g K85, 4 g corn oil (placebo), or 12 g TG30		
Diagnosis and criteria for inclusion: Healthy male volunteers between 18 and 55 years of age and within 15% of their ideal body weight according to the Metropolitan Life Insurance Company, 1983. Subjects giving informed consent.		
Test product, dose and mode of administration, batch no.: K85, 4 soft gelatin capsules of 1g taken orally ActiEPA 30 (TG30), a triglyceride formula with 30 % n-3 fatty acids, 12 soft gelatin capsules of 1g taken orally		
Duration of treatment: 7 weeks		
Reference therapy, dose and mode of administration, batch no.: Corn oil, 4 soft gelatin capsules of 1g taken orally		
Criteria for evaluation: - Fatty acid analysis of the phospholipid- and cholesteryl ester fractions of the plasma. - Analysis of serum total-, HDL-, LDL-, VLDL- cholesterol and triglycerides. - Several fibrinolysis and coagulation assays.		
Statistical methods: Statistical significance of differences between means was estimated by Student's t-test and a p-value < 0.05 was considered statistically significant. Simple linear regression was performed to calculate regression lines and correlations. Results are presented		

b(4)

Study code:

CK85-007 cont.

SUMMARY: An initial tendency of delayed incorporation of EPA was observed with K85. The difference disappeared at the end of the intervention period. K85 gave a more efficient displacement of arachidonic acid in plasma phospholipids and especially cholesteryl esters. The main blood lipids were not influenced differently by the two compounds K85 and TG30. Both formulas had an inhibitory effect on collagen-induced platelet aggregation and TxB_2 formation in whole blood.

An 8-11% increase in tissue-factor pathway inhibitor was seen during intervention which was associated with minor alterations in total- and LDL cholesterol, but not with any alterations in the fatty acid pattern in plasma.

CONCLUSIONS: Both EPA and DEA from K85 and TG30 were well incorporated into plasma phospholipids. A similar beneficial influence on hemostasis in men is indicated. Four grams daily of K85 for 7 weeks is well tolerated.

Appears This Way
On Original

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85 Name of Active Ingredients: EPA and DHA		
Title of Study: An Efficacy Study with Different Doses of K85 Omega-3 Fatty Acids Ethyl Ester Concentrate in Hyperlipidemic Patients		
Principal Investigators: T Kjellström, MD, and M Thorngren, MD, PhD		
Study Centers: General Hospital of Malmö, Malmö, SE (Kjellström) and University Hospital of Lund, Lund, SE (Thorngren)		
Publication (reference): None		
Studied period (years): 1.3 years First subject randomized: January 15, 1990 Last subject completed: April 17, 1991	Phase of development: Phase II	
Objectives: This trial was designed to investigate the effect of K85 2 g per day, 4 g per day, and 8 g per day in subjects with hyperlipidemia after treatment with a therapeutic diet. The protocol-specified primary objective was the change in serum triglyceride (TG) levels. Protocol-specified secondary objectives included changes in serum total cholesterol (TC) levels, high-density lipoprotein cholesterol (HDL-C) levels, and free fatty acid (FFA) profiles.		
Methodology: This study was a multicenter, randomized, parallel-group, placebo-controlled study of K85 2 g per day, 4 g per day, and 8 g per day administered orally to subjects with hyperlipidemia. Subjects underwent an 8-week Dietary Run-In Period, in which they were asked to follow a therapeutic diet designed to decrease energy intake, followed by an 8-week Treatment Period with K85 2 g per day; K85 4 g per day, K85 8 g per day, or placebo (corn oil) capsules.		
Number of subjects (planned and analyzed): The planned sample size was 64 subjects with approximately 16 subjects in each treatment arm. The actual sample size was 69 subjects. These subjects were randomly assigned to receive K85 2 g per day, K85 4 g per day, K85 8 g per day, or placebo (corn oil; 4 g per day) based on a computer-generated randomization scheme.		
Of the 69 subjects who were randomized, 17 received K85 2 g per day, 17 received K85 4 g per day, 18 received K85 8 g per day, and 17 received placebo (corn oil; 4 g per day). A total of 67 subjects (16 subjects in the K85 2-g treatment group, 16 subjects in the K85 4-g treatment group, 18 subjects in the K85 8-g treatment group, and 17 subjects in the placebo treatment group) were included in the intent-to-treat (ITT) analysis. Six subjects were withdrawn from the study. The per-protocol (PP) population consisted of 9 subjects in the K85 2-g treatment group, 12 subjects in the K85 4-g treatment group, 6 subjects in the K85 8-g treatment group, and 13 subjects in the placebo treatment group.		

Appears This Way
On Original

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Diagnosis and main criteria for inclusion or exclusion: Male or female subjects were included in this study if they were between 18 and 70 years of age; if they had mean fasting serum TG levels between 177 and 442 mg/dL (inclusive) and mean fasting TC levels of at least 250 mg/dL, determined using at least 2 measurements obtained more than 1 week apart during the Dietary Run-In Period; if they followed dietary recommendations and completed the Dietary Run-In Period; and if they signed the informed consent form (ICF). Subjects were excluded from this study if they had diabetes mellitus or psychological disease; if they had a myocardial infarction or other serious illness within 6 months of entering the study; if they had received treatment with lipid-lowering drugs during the Dietary Run-In Period; if they had received another medical treatment (eg, anticoagulant therapy) that may have interfered with the effect of K85; if they were pregnant or were lactating mothers; or if they abused drugs or alcohol.		
Test product, dose and mode of administration, lot number: Subjects assigned to receive K85 2 g per day received two 1-g capsules of K85 daily. Subjects assigned to receive K85 4 g per day received four 1-g capsules daily. Subjects assigned to receive K85 8 g per day received eight 1-g capsules daily. K85 2 g, 4 g, or 8 g per day was administered as one daily dose or as two equal daily doses. Lot number 21352 with an expiration date of April 1991 was used for this study.		
Reference therapy, dose and mode of administration, lot number: Subjects assigned to the placebo arm received four 1-g capsules of corn oil daily, administered as one daily dose or as two equal daily doses. Lot number 21354 with an expiration date of April 1991 was used for this study.		
Criteria for evaluation: Efficacy: The primary efficacy endpoint was the change in serum TG levels. Secondary efficacy endpoints included changes in serum TC, HDL-C, LDL-C, Apo-A1, Apo-B, and Lp(a) levels.		
Safety: Safety was assessed through the monitoring of treatment-emergent adverse events (AEs), treatment-emergent serious adverse events (SAEs), concomitant medications, vital signs, body weight, and laboratory assessments.		
Statistical methods: Data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. Primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analyses, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Kruskal-Wallis test was used to compare median changes and median percentage changes between treatment groups. All statistical tests of significance were 2-tailed with a 5% significance level.		

**Appears This Way
On Original**

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		

Summary–Conclusions

Efficacy Results: Efficacy results for the PP population are presented in the tables below.

Summary of Efficacy Results, Relative Changes (Per-Protocol Population)

Efficacy Endpoint	K85 2 g (N = 9) (Median, %)	K85 4 g (N = 12) (Median, %)	K85 8 g (N = 6) (Median, %)	Total (N = 27) (Median, %)	Placebo (N = 13) (Median, %)	P-value*
Primary Efficacy Endpoint						
Change in serum TG level	-12.2	-30.0	-43.2	-32.8	-8.2	0.1448
Secondary Efficacy Endpoints						
Change in TC level	-2.3	6.9	1.9	3.3	-2.7	0.0968
Change in HDL-C level	0.0	10.7	2.3	3.6	7.7	0.1886
Change in LDL-C level	1.6	13.7	9.0	11.2	2.8	0.1028
Change in Apo-A1 level	-2.041	-3.401	-6.292	-3.846	-1.786	0.5250
Change in Apo-B level	0.568	8.419	8.242	6.452	-3.465	0.0998
Change in Lp(a) level	-1.031	18.796	32.986	8.025	-5.040	0.0773

* Nonparametric P-values were computed using a Kruskal-Wallis test to evaluate the overall treatment effect between groups.

Summary of Efficacy Results, Absolute Changes (Per-Protocol Population)

Efficacy Endpoint	K85 2 g (N = 9) (Median)	K85 4 g (N = 12) (Median)	K85 8 g (N = 6) (Median)	Total (N = 27) (Median)	Placebo (N = 13) (Median)	P-value*
Primary Efficacy Endpoint						
Change in serum TG level (mg/dL)	-25.0	-87.0	-99.5	-81.0	-15.0	0.1223
Secondary Efficacy Endpoints						
Change in TC level (mg/dL)	-6.0	17.0	5.0	11.0	-10.0	0.0687
Change in HDL-C level (mg/dL)	0.0	3.0	0.5	1.0	2.0	0.1910
Change in LDL-C level (mg/dL)	3.0	25.5	21.0	22.0	6.0	0.1569
Change in Apo-A1 level (g/L)	-0.020	-0.035	-0.065	-0.040	-0.020	0.5533
Change in Apo-B level (g/L)	0.010	0.125	0.125	0.100	-0.070	0.0966
Change in Lp(a) level (g/L)	-0.050	0.140	0.555	0.100	-0.015	0.1098

* Nonparametric P-values were computed using a Kruskal-Wallis test to evaluate the overall treatment effect between groups.

Safety Results: Comparable numbers of subjects in each K85 treatment group had treatment-emergent AEs (4 subjects with 5 treatment-emergent AEs in the K85 2-g treatment group, 7 subjects with 10 treatment-emergent AEs in the K85 4-g treatment group, and 6 subjects with 11 treatment-emergent AEs in the K85 8-g treatment group). Two subjects in the placebo treatment group had 2 treatment-emergent AEs. The majority of treatment-emergent AEs were in the digestive body system and were considered mild-to-moderate in intensity. Although drug relationships were not reported on the CRFs, in this report, all treatment-emergent AEs were classified as related to study drug.

No subjects died or had any treatment-emergent SAEs during this study. One subject in the K85 2-g treatment group and 2 subjects in the K85 4-g treatment group discontinued the study due to treatment-emergent AEs.

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Conclusions: Absolute and relative changes in serum TG levels and other lipid levels (TC, HDL-C, LDL-C, Apo-A1, Apo-B, and Lp[a] levels) were not significantly different between treatment groups. During this study, K85 was safe and well tolerated at all dose levels. Date of the report: April 11, 2003		

Appears This Way
On Original

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Title of Study: Effect of K85 and Corn Oil in Hyperlipidemic Patients – A Multicenter Study		
Principal Investigators: L. Borthwick, MB ChB, MRCP; P. Durrington, FRCP, MD, MRCP, MB ChB; J. Miller, DPhil, FRCP, MSc, MRCP MD, MB ChB; D. Galton, FRCP, MD, MRCP, MSc, MB BS; M. Laker, FRCPATH, MD, MRCPATH, MB BS; J. Reckless, FRCP, MD, MRCP, MB BS; S. Iverson, MRCPATH, MB BS; D. Sheldon, MRCP, MB BS; G. McGregor, MB ChB		
Study Centers: Lister Hospital, Stevenage, UK (Borthwick); Manchester Royal Infirmary, Manchester, UK and Withington Hospital, Manchester, UK (Durrington and Miller); St Bartholomew's Hospital, London, UK (Galton); Royal Victoria Hospital, Newcastle-Upon-Tyne, UK (Laker); Royal United Hospital, Bath, UK (Reckless); Royal Sussex County Hospital, Brighton, UK (Iverson); Newton-Aycliffe Health Center, Co. Durham, UK and The Health Center, Co. Durham, UK (Sheldon and McGregor)		
Publication (reference): Mackness MI, Bhatnagar D, Durrington PN. Effects of a new fish oil concentrate on plasma lipids and lipoproteins in patients with hypertriglyceridaemia. Eur J Clin Nutr 1994 Dec;48(12):859-65.		
Studied period (years): 1.3 years First subject enrolled: April 17, 1990 Last subject completed: August 28, 1991	Phase of development: Phase III	
Objectives: This trial was designed to investigate the effect of K85 4 g per day in subjects with hyperlipidemia. The primary protocol-specified objective was to compare the effect of K85 4 g per day with placebo (corn oil) on serum triglyceride (TG), total cholesterol (TC), and high-density lipoprotein cholesterol (HDL-C) levels in subjects with persisting hyperlipidemia after treatment with a therapeutic diet. The secondary protocol-specified objective was to compare the tolerability of K85 4 g per day with placebo (corn oil) in subjects with hyperlipidemia.		
Methodology: This study was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of K85 4 g per day administered orally to subjects with hyperlipidemia. Subjects underwent a 10-week Dietary Run-In Period, in which they were asked to follow a diet based on the European Atherosclerosis Society lipid-lowering diet, followed by a 12-week Treatment Period with either K85 4 g per day or placebo (corn oil) capsules.		
Number of subjects (planned and analyzed): The planned sample size was 100 subjects with approximately 50 subjects in each treatment arm. The actual sample size was 111 subjects. These subjects were randomly assigned to receive either K85 4 g per day or placebo (corn oil) based on a computer-generated randomization scheme. Of the 111 subjects who were randomized, 54 received K85 4 g per day and 57 received placebo (corn oil). A total of 105 subjects (52 subjects in the K85 4-g treatment group and 53 subjects in the placebo group) were included in the intent-to-treat (ITT) analysis. Fifteen subjects were withdrawn from the study. The corresponding per-protocol (PP) population consisted of 49 subjects in the K85 4-g treatment group and 46 subjects in the placebo treatment group.		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Diagnosis and main criteria for inclusion or exclusion: Male or female subjects were included in this study if they were between 18 and 70 years of age; if they had a history of hyperlipidemia and were receiving medication for hyperlipidemia but, in the opinion of the principal investigator, could have their medication withdrawn for the duration of this study, or they had hyperlipidemia despite dietary therapy, or they were newly diagnosed with hyperlipidemia; if they had mean fasting total serum TG levels between 177 and 885 mg/dL (inclusive) and mean fasting TC levels of at least 201 mg/dL during the final 2 weeks of the Dietary Run-In Period; if fasting serum TG and TC values did not differ by more than 50% during the final 2 weeks of the Dietary Run-In Period; and if they signed the informed consent form (ICF). Subjects were excluded from this study if they had diabetes mellitus (defined as a fasting blood glucose level higher than 126 mg/dL), known hypothyroidism, or a severe concurrent illness (including serious psychiatric disease); if they had a myocardial infarction or other serious illness within 3 months of entering the study; if their body weight was more than 135% of their ideal body weight (according to the 1983 Metropolitan Height and Mass Tables) or a body weight change less than 2.2 pounds per week between start and finish of the Dietary Run-In Period; if they had been advised to consume fewer than 1500 kcal per day; if they were pregnant, if they were of childbearing age but were not using active contraceptive precautions, or if they were lactating mothers; or if they had known history of drug or alcohol abuse.</p>		
<p>Test product, dose and mode of administration, lot number: Subjects assigned to the K85 4-g treatment group received four 1-g capsules of K85 daily, administered orally as either one 4-g dose or two 2-g doses. Lot number 26845 with an expiration date of April 1992 was used for this study.</p>		
<p>Reference therapy, dose and mode of administration, lot number: Subjects assigned to the placebo treatment group received four 1-g capsules of corn oil daily, administered orally as either one 4-g dose or two 2-g doses. Lot number 26846 with an expiration date of April 1992 was used for this study.</p>		
<p>Criteria for evaluation: Efficacy: The primary efficacy endpoint was the change from baseline to end of study in serum TG levels. Secondary efficacy endpoints included changes from baseline to end of study in TC, HDL-C, low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (Apo-A1), and apolipoprotein B (Apo-B) levels.</p>		
<p>Safety: Safety was assessed through the monitoring of treatment-emergent adverse events (AEs), treatment-emergent serious adverse events (SAEs), concomitant medications, vital signs, body weight, and laboratory assessments.</p>		
<p>Statistical methods: Data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. Primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analyses, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Wilcoxon two-sample test was used to compare median changes and median percentage changes between treatment groups. All statistical tests of significance were 2-tailed with a 5% significance level.</p>		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>	
			Name of Finished Product: K85
			Name of Active Ingredients: EPA and DHA

Summary- Conclusions

Efficacy Results: Efficacy results for the PP population are presented in the tables below:

Summary of Efficacy Results, Relative Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4-g (N = 49) (Median, %)	Placebo (N = 46) (Median, %)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level	-25.4	0.5	<0.0001
Secondary Efficacy Endpoint			
Change in TC level	-1.1	0.0	0.8816
Change in HDL-C level	0.0	4.0	0.9576
Change in LDL-C level	4.8	0.9	0.1349
Change in Apo-A1 level	-1.869	0.971	0.4450
Change in Apo-B level	2.632	2.564	0.7669

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Summary of Efficacy Results, Absolute Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4-g (N = 49) (Median)	Placebo (N = 46) (Median)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level (mg/dL)	-60.0	1.0	<0.0001
Secondary Efficacy Endpoint			
Change in TC level (mg/dL)	-4.0	0.0	0.8376
Change in HDL-C level (mg/dL)	0.0	2.0	0.9118
Change in LDL-C level (mg/dL)	9.0	2.0	0.0920
Change in Apo-A1 level (g/L)	-0.020	0.010	0.4549
Change in Apo-B level (g/L)	0.030	0.030	0.8087

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Appears This Way
On Original

Name of Company: Pronova Biocare a.s.	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Safety Results: More subjects in the K85 4-g treatment group than the placebo treatment group had treatment-emergent AEs (28 subjects with 59 AEs in the K85 4-g treatment group and 24 subjects with 40 AEs in the placebo treatment group). The majority of these AEs were considered mild-to-moderate in intensity. No more than 2 subjects in either treatment group had any single treatment-emergent AE that was considered severe. Additionally, comparable numbers of subjects in each treatment group had treatment-emergent AEs that were considered related to study drug (12 subjects with 16 AEs in the K85 4-g treatment group and 10 subjects with 16 AEs in the placebo treatment group).</p> <p>One subject in the placebo treatment group died during the study, and 1 subject in the K84 treatment group died 16 days following study completion. The death in the K85 4-g treatment group was considered related to study drug (because actual relationship was not recorded on the case report form [CRF]), and the death in the placebo group was considered unrelated to study drug. Six subjects in the K85 4-g treatment group and 3 subjects in the placebo treatment group had treatment-emergent SAEs. Two of these SAEs (both in the K85 4-g treatment group) were considered related to study drug. Three subjects in the K85 4-g treatment group and 3 subjects in the placebo treatment group discontinued the study due to treatment-emergent AEs.</p> <p>No subject had any shift from baseline to a toxicity grade greater than 1.</p>		
<p>Conclusions: Compared with subjects in the placebo treatment group, subjects in the K85 4-g treatment group had significantly larger absolute and relative reductions in serum TG.</p> <p>During this study, K85 4 g per day was considered safe and well tolerated.</p> <p>Date of the report: April 11, 2003</p>		

Appears This Way
On Original

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Title of Study: Effect of K85 and Corn Oil in Hyperlipidemic Patients: A Multicenter Study		
Principal Investigators: LJ Borthwick, MB, ChB, MRCP; R Cramb, MB, ChB, MRCP; R Wray, MB, ChB, MRCP; AF Jones, MA, MB, BChir, DPhil, MRCP; and MJ Toop, MA, MB, BChir, MRCP, MRCPPath		
Study Centers: Lister Hospital, Stevenage, Hertfordshire, UK (Borthwick); Queen Elizabeth Hospital, Birmingham, UK (Cramb); Hastings Health Authority, Hastings, East Sussex, UK (Wray); East Birmingham Hospital, Birmingham, UK (Jones); and Harrogate General Hospital, Harrogate, UK (Toop)		
Publication (reference): Borthwick L. The effects of an omega-3 ethyl ester concentrate on blood lipid concentrations in patients with hyperlipidaemia. The UK Study Group. Clin Drug Invest 1998 May;15(5): 397-404.		
Studied period (years): 1.5 years First subject enrolled: March 5, 1991 Last subject completed: September 22, 1992	Phase of development: Phase III	
Objectives: This trial was designed to investigate the effect of K85 4 g per day in subjects with hyperlipidemia. The protocol-specified objectives were to evaluate the effect of K85 4 g per day with placebo (corn oil) on serum TG, TC, and HDL-C levels and to compare the tolerability of K85 4 g per day with placebo (corn oil) in subjects who continue to suffer from hyperlipidemia after treatment with a therapeutic diet.		
Methodology: This study was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of K85 4 g per day administered orally to subjects with hyperlipidemia. Subjects underwent a 10-week Dietary Run-In Period, in which they were asked to follow the European Atherosclerosis Society lipid-lowering diet, followed by a 12-week Treatment Period with either K85 4 g per day or placebo (corn oil) capsules.		
Number of subjects (planned and analyzed): The planned sample size was 50 subjects with approximately 25 subjects in each treatment arm. The actual sample size was 52 subjects. These subjects were randomly assigned to receive either K85 4 g per day or placebo (corn oil) based on a computer-generated randomization scheme.		
Of the 55 subjects who were randomized, 29 were in the K85 4-g treatment group and 26 were in the placebo treatment group. All subjects randomized during this study were included in the intent-to-treat (ITT) analysis except for 2 subjects in the placebo treatment group who withdrew from the study. Two subjects in the K85 4-g treatment group were withdrawn from the study due to adverse events, and 3 subjects in the K85 4-g treatment group and 1 subject in the placebo treatment group were withdrawn due to noncompliance. Two subjects in the placebo treatment group withdrew for other reasons. The corresponding per-protocol (PP) population consisted of 24 subjects in the K85 4-g treatment group and 23 subjects in the placebo treatment group.		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Diagnosis and main criteria for inclusion or exclusion: Male or female subjects were included in this study if they were between 18 and 70 years of age; if they had a history of hyperlipidemia and were receiving medication for this hyperlipidemia but, in the opinion of the investigator, could have their medication withdrawn for the duration of the study, or they had hyperlipidemia despite dietary therapy, or they had newly diagnosed hyperlipidemia; if they had mean fasting serum triglyceride (TG) levels between 177 and 885 mg/dL (inclusive) and mean total fasting cholesterol (TC) levels of at least 201 mg/dL during the final 2 weeks of the Dietary Run-In Period; if fasting serum TG and TC values did not differ by more than 50% during the final 2 weeks of the Dietary Run-In Period; if they had change in body weight of less than 2.2 pounds per week during the 10-week Dietary Run-In Period (Weeks -10 through -2 [Visits 1 through 3]); and if they signed the informed consent form (ICF). Subjects were excluded from this study if they had diabetes mellitus (defined as a fasting blood glucose level higher than 126 mg/dL), known hypothyroidism, or a severe concurrent illness (including serious psychiatric disease); if they had a myocardial infarction or other serious illness within 3 months of entering the study; if their body weight was more than 135% of their ideal body weight (according to the 1983 Metropolitan Height and Mass Tables); if they were advised to consume less than 1500 kcal per day; if they abused alcohol or drugs; if they were pregnant, if they were of childbearing age but were not using active contraceptive precautions, or if they were lactating mothers.</p>		
<p>Test product, dose and mode of administration, lot number: Subjects assigned to the K85 treatment arm received four 1-g capsules of K85 daily, administered orally as either one 4-g dose or as two 2-g doses. Lot number 27236 with an expiration date of October 1992 was used for this study.</p>		
<p>Reference therapy, dose and mode of administration, lot number: Subjects assigned to the placebo arm received four 1-g capsules of corn oil daily, administered orally as either one 4-g dose or as two 2-g doses. Lot number 27238 with an expiration date of October 1992 was used for this study.</p>		
<p>Criteria for evaluation: Efficacy: The primary efficacy endpoint was the change from baseline to end of study in serum TG levels. Secondary efficacy endpoints included changes from baseline to end of study in TC, HDL-C, and LDL-C levels.</p>		
<p>Safety: Safety was assessed through the monitoring of treatment-emergent adverse events (AEs), treatment-emergent serious adverse events (SAEs), concomitant medications, vital signs, body weight, and laboratory assessments.</p>		
<p>Statistical methods: Data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. Primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analyses, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Wilcoxon two-sample test was used to compare median changes and median percentage changes between treatment groups. All statistical tests of significance were 2-tailed with a 5% significance level.</p>		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		

Summary–Conclusions

Efficacy Results: Efficacy results for the PP population are presented in the tables below:

Summary of Efficacy Results, Relative Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4 g (N = 24) (Median, %)	Placebo (N = 23) (Median, %)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level	-32.4	10.5	<0.0001
Secondary Efficacy Endpoint			
Change in TC level	-1.6	-1.6	0.8648
Change in HDL-C level	3.8	0.0	0.9066
Change in LDL-C level	7.5	-0.6	0.0310

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Summary of Efficacy Results, Absolute Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4 g (N = 24) (Median, mg/dL)	Placebo (N = 23) (Median, mg/dL)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level	-84.0	30.0	<0.0001
Secondary Efficacy Endpoint			
Change in TC level	-4.0	-4.0	0.7736
Change in HDL-C level	1.5	0.0	1.0000
Change in LDL-C level	11.5	-1.0	0.0320

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Safety Results: More subjects in the K85 4-g treatment group than in the placebo treatment group had treatment-emergent AEs (19 subjects with 35 AEs versus 11 subjects with 19 AEs, respectively). The majority of these AEs were considered mild-to-moderate in intensity. No more than 2 subjects in either treatment group had any single treatment-emergent AE that was considered severe. More subjects in the K85 4-g treatment group than in the placebo treatment group had treatment-emergent AEs that were considered related to study drug (12 subjects with 17 drug-related events versus 6 subjects with 7 drug-related events, respectively).

No subjects died during this study. One subject in the K85 4-g group and 1 subject in the placebo treatment had treatment-emergent SAEs of angina pectoris. The subject in the placebo treatment group was hospitalized later for angiography. These SAEs were considered unrelated to study drug. Two subjects in the K85 4-g treatment group discontinued the study due to treatment-emergent AEs.

No subject had a shift from baseline in any laboratory parameter to a toxicity grade greater than grade 1.

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Conclusions: Compared with subjects in the placebo treatment group, subjects in the K85 4-g treatment group had significantly different absolute and relative median changes in serum TG. Compared with subjects in the placebo treatment group, subjects in the K85 4-g treatment group had significantly different absolute and relative median changes in LDL-C. For the K85 treatment group, the median baseline LDL-C value was within borderline high range (National Cholesterol Education Program Adult Treatment Panel [NCEP ATP] III borderline high range: 130-159 mg/dL) and the median end-of-study value was within high range (NCEP ATP III high range: 160-189 mg/dL).</p> <p>During this study, K85 4 g per day was considered safe and well tolerated.</p> <p>Date of the report: April 11, 2003</p>		

Appears This Way
On Original

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Title of Study: Effect of K85 Omega-3 Fatty Acids Ethyl Ester Concentrate and Corn Oil in Postmyocardial Infarction Patients with Hypertriglyceridemia		
Principal Investigators: Anders G Olsson, MD, PhD		
Study Center: Linköping Hospital, Linköping, Sweden		
Publication (reference): Swahn E, von Schenck H, Olsson AG. Omega-3 ethyl ester concentrate decreases total apolipoprotein CIII and increases antithrombin III in postmyocardial infarction patients. Clin Drug Invest 1998;15(6):473-82.		
Studied period (years): 1.75 years First subject enrolled: June 12, 1990 Last subject completed: March 13, 1992	Phase of development: Phase III	
Objectives: This trial was designed to investigate the effect of K85 in subjects with a previous myocardial infarction (MI) and with HTG despite treatment with a therapeutic diet. The protocol-specified primary objective was to compare the change in serum triglyceride (TG) levels between subjects treated with K85 4 g per day and subjects treated with placebo (corn oil).		
Methodology: This study was a single-center, randomized, double-blind, parallel-group, placebo-controlled study of K85 4 g per day administered orally to subjects who had a previous MI and HTG. Subjects underwent a 9-week Dietary Run-In Period, in which they were asked to follow general dietary advice from the American Heart Association (AHA) and the European Atherosclerosis Society lipid-lowering diets, followed by a 12-week Treatment Period with either K85 4 g per day or placebo (corn oil) capsules.		
Number of subjects (planned and analyzed): The planned sample size was 50 subjects with approximately 25 subjects in each treatment arm. The actual sample size was 53 subjects. These subjects were randomly assigned to receive either 4 g per day or placebo (corn oil) based on a computer-generated randomization scheme. Of the 53 subjects who were randomized, 26 received K85 4 g per day and 27 received placebo (corn oil). All of the subjects randomized during this study were included in the intent-to-treat (ITT) analysis except for 1 subject from the placebo treatment group who was withdrawn from the study due to difficulties in swallowing the study medication. The corresponding per-protocol (PP) population consisted of 26 subjects in the K85 4-g treatment group and 26 subjects in the placebo treatment group.		
Diagnosis and main criteria for inclusion or exclusion: Male or female subjects were included in the study if they were between 18 and 70 years of age, if they had a previous MI, if they had HTG despite dietary therapy, if they had mean fasting serum TG levels between 177 and 885 mg/dL and mean fasting total cholesterol (TC) levels no higher than 386 mg/dL during the final 2 weeks of the Dietary Run-In Period, if serum TG and TC levels did not differ by more than 50% during the final 2 weeks of the Dietary Run-In Period, if they had a body weight change less than 2.2 pounds per week during the Dietary Run-In Period, and if they signed the informed consent form (ICF). Subjects were excluded from this study if they had type 1 diabetes mellitus, if they had MI or other serious illness within 3 months of entering the study, if they had a severe concurrent illness (including serious psychiatric disease), if they abused alcohol or drugs, or if females of childbearing age were pregnant, lactating, or not using active contraceptive precautions.		

Name of Company: Pronova Biocare a.s.	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Test product, dose and mode of administration, lot number: Subjects assigned to the K85 treatment arm received four 1-g capsules of K85 daily, administered orally as either one 4-g dose or as two 2-g doses. Lot number 26845 with an expiration date of April 1992 was used for this study.		
Reference therapy, dose and mode of administration, lot number: Subjects assigned to the placebo arm received four 1-g capsules of corn oil daily, administered orally as either one 4-g dose or as two 2-g doses. Lot number 26846 with an expiration date of April 1992 was used for this study.		
Criteria for evaluation: Efficacy: The primary efficacy endpoint was the change from baseline to end of study in serum TG levels. Secondary efficacy endpoints included changes from baseline to end of study in TC, HDL-C, LDL-C, VLDL-C, Apo-A1, Apo-B, and Lp(a) levels.		
Safety: Safety was assessed through the monitoring of treatment-emergent adverse events (AEs), treatment-emergent serious adverse events (SAEs), concomitant medications, vital signs, heart rate, physical examination, body weight, and laboratory assessments.		
Statistical methods: Data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. Primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analyses, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Wilcoxon two-sample test was used to compare median changes and median percentage changes between treatment groups. All statistical tests of significance were 2-tailed with a 5% significance level.		

Appears This Way
On Original

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		

Summary--Conclusions

Efficacy Results: Efficacy results for the PP population are presented in the tables below.

Summary of Efficacy Results, Relative Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4-g (N = 26) (Median, %)	Placebo (N = 26) (Median, %)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level	-17.3	-4.4	0.0033
Secondary Efficacy Endpoints			
Change in TC level	-2.7	0.4	0.5520
Change in HDL-C level	4.9	0.0	0.4753
Change in LDL-C level	7.2	-3.5	0.0451
Change in VLDL-C level	-26.9	5.0	0.0178
Change in Apo-A1 level	-3.333	3.667	0.0433
Change in Apo-B level	0.785	-2.238	0.2682
Change in Lp(a) level	-1.408	-1.031	0.9073

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Summary of Efficacy Results, Absolute Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4-g (N = 26) (Median)	Placebo (N = 26) (Median)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level (mg/dL)	-43.0	-10.0	0.0052
Secondary Efficacy Endpoints			
Change in TC level (mg/dL)	-5.5	1.0	0.6340
Change in HDL-C level (mg/dL)	1.5	0.0	0.4465
Change in LDL-C level (mg/dL)	10.5	-6.0	0.0232
Change in VLDL-C level (mg/dL)	-9.5	2.0	0.0261
Change in Apo-A1 level (g/L)	-0.040	0.045	0.0653
Change in Apo-B level (g/L)	0.015	-0.035	0.3411
Change in Lp(a) level (g/L)	-0.060	-0.010	0.9536

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Safety Results: In the K85 4-g treatment group, 2 subjects experienced 2 treatment-emergent AEs which were considered unrelated to study drug. In the placebo treatment group, 4 subjects had 4 treatment-emergent AEs; 2 of these treatment-emergent AEs were considered related to study drug. All treatment-emergent AEs were considered mild-to-moderate in intensity. One subject had a treatment-emergent AE for which the intensity was not recorded on the CRF. One subject in the placebo treatment group discontinued the study due to a treatment-emergent AE of problems swallowing study medication.</p> <p>No subjects died or had any treatment-emergent SAEs in this study.</p> <p>Fourteen subjects (9 subjects in the K85 4-g treatment group and 5 subjects in the placebo treatment group) had 16 shifts from baseline in laboratory parameters from a lower toxicity grade to a higher toxicity grade. In the K85 4-g treatment group, 1 subject had 1 shift from grade 0 to high range, 7 subjects had 9 shifts from grade 0 to grade 1, and 1 subject had 1 shift from grade 1 to grade 2. In the placebo treatment group, 2 subjects had 2 shifts from grade 0 to high range, 2 subjects had 2 shifts from grade 0 to grade 1, and 1 subject had 1 shift from grade 0 to grade 2. No subject had any shift from baseline to a toxicity grade greater than 2.</p>		
<p>Conclusions: Compared with subjects in the placebo treatment group, subjects in the K85 4-g treatment group had significantly larger absolute and relative reductions in serum TG. Correspondingly, subjects in the K85 4-g treatment group also had absolute and relative reductions in VLDL-C, while subjects in the placebo treatment group had absolute and relative increases in VLDL-C. These changes were significant between treatment groups. The K85 4-g treatment group also had significantly different relative changes in Apo-A1 compared with the placebo treatment group.</p>		
<p>Compared with subjects in the placebo treatment group, subjects in the K85 4-g treatment group had significantly larger absolute and relative changes in LDL-C. For the K85 4-g treatment group, the median baseline LDL-C value was within the borderline high range (NCEP ATP III borderline high range: 130-159 mg/dL) and the median end-of-study value was within the high range (NCEP ATP III high range: 160-189 mg/dL).</p>		
<p>During this study, K85 4 g per day was considered safe and well tolerated.</p>		
<p>Date of the report: April 11, 2003</p>		

Appears This Way
On Original

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85 Name of Active Ingredients: EPA and DHA		
Title of Study: Effect of K85 Omega-3 Fatty Acids Ethyl Ester Concentrate and Corn Oil in Patients with Hyperlipidemia		
Principal Investigator: Olov Wiklund		
Study Center: Sahlgrenska (Sahlgren's) University Hospital, Gothenburg, SE		
Publication (reference): None		
Studied period (years): 1.7 years First subject enrolled: October 11, 1990 Last subject completed: June 22, 1992	Phase of development: Phase III	
Objectives: This trial was designed to investigate the effect of K85 4 g per day in subjects with hyperlipidemia. The protocol-specified objective was to compare the effect of K85 4 g per day with placebo (corn oil) on serum lipid concentrations in subjects who after treatment with diet have hyperlipidemia.		
Methodology: This was a single-center, randomized, double-blind, parallel-group, placebo-controlled study of K85 4 g per day administered orally to subjects with hyperlipidemia. Subjects underwent a 9-week Dietary Run-In Period during which they were asked to follow a diet based on the American Heart Association and the European Atherosclerosis Society lipid-lowering diets, followed by a 12-week Treatment Period with either K85 4 g per day or placebo (corn oil) capsules.		
Number of subjects (planned and analyzed): The planned sample size was 60 subjects with approximately 30 subjects in each treatment arm. The actual sample size was 60 subjects. These subjects were randomly assigned to receive either K85 4 g per day or placebo (corn oil) based on a computer-generated randomization scheme. Of the 60 subjects who were randomized, 30 received K85 4 g per day and 30 received placebo (corn oil). All subjects were included in the intent-to-treat (ITT) analysis. Two subjects in the K85 4-g treatment group were withdrawn from the study. The corresponding per-protocol (PP) population consisted of 28 subjects in the K85 4-g treatment group and 30 subjects in the placebo treatment group.		
Diagnosis and main criteria for inclusion or exclusion: Male or female subjects were included in this study if they were between 18 and 70 years of age; if they had hyperlipidemia despite dietary therapy, or they were newly diagnosed with hyperlipidemia, or they had a history of hyperlipidemia and were receiving medication for hyperlipidemia, but in the opinion of the principal investigator, could have their medication withdrawn for the duration of this study; if they had mean fasting serum triglyceride (TG) levels between 177 and 885 mg/dL (inclusive) and mean fasting total cholesterol (TC) levels of at least 232 mg/dL during the final 2 visits of the Dietary Run-In Period; if fasting serum TG and TC values did not differ by more than 50% during the final 2 visits of the Dietary Run-In Period; and if they signed the informed consent form (ICF). Subjects were excluded from this study if they had a fasting TC level higher than 386 mg/dL; if they had diabetes mellitus type 1 or a severe concurrent illness (including serious mental disease); if they had a myocardial infarction or other serious illness within 3 months of entering the study; if they had been advised to consume fewer than 1500 kcal per day; if they had known history of drug or alcohol abuse; if they were pregnant or lactating females or women of childbearing potential not using active contraceptive precautions.		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Test product, dose and mode of administration, lot number: Subjects assigned to the K85 4-g treatment group received four 1-g capsules of K85 daily, administered orally as either one 4-g dose or two 2-g doses. Medication lot number 26845 with an expiration date of April 1992 was used for this study.		
Reference therapy, dose and mode of administration, lot number: Subjects assigned to the placebo treatment group received four 1-g capsules of corn oil daily, administered orally as either one 4-g dose or two 2-g doses. Medication lot number 26846 with an expiration date of April 1992 was used for this study.		
Criteria for evaluation:		
Efficacy: The primary efficacy endpoint was the change from baseline to end of study in serum TG levels. Secondary efficacy endpoints included changes from baseline to end of study in TC, HDL-C, LDL-C, VLDL-C, Apo-A1, Apo-B, and Lp(a) levels.		
Safety: Safety was assessed through the monitoring of treatment-emergent adverse events (AEs), treatment-emergent serious adverse events (SAEs), concomitant medications, vital signs, body weight, and clinical laboratory assessments.		
Statistical methods: Data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. Primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analyses, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Wilcoxon two-sample test was used to compare median changes and median percentage changes between treatment groups. All statistical tests were 2-tailed with a 5% significance level.		

**Appears This Way
On Original**

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85	Volume:	
Name of Active Ingredients: EPA and DHA	Page:	

Summary–Conclusions

Efficacy Results: Efficacy results for the PP population are presented in the table below:

Summary of Efficacy Results, Relative Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4 g (N = 28) (Median, %)	Placebo (N = 30) (Median, %)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level	-28.7	-6.5	0.0013
Secondary Efficacy Endpoints			
Change in TC level	-2.0	1.1	0.5543
Change in HDL-C level	-1.0	3.9	0.8519
Change in LDL-C level	4.1	-0.7	0.1591
Change in VLDL-C level	-25.2	-2.1	0.0423
Change in Apo-A1 level	-3.294	1.027	0.2132
Change in Apo-B level	-0.633	0.000	0.9876
Change in Lp(a) level	0.000	0.000	0.7977

^a P-values were computed using nonparametric Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Summary of Efficacy Results, Absolute Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4 g (N = 28) (Median)	Placebo (N = 30) (Median)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level (mg/dL)	-69.5	-23.5	0.0022
Secondary Efficacy Endpoints			
Change in TC level (mg/dL)	-6.0	3.0	0.4550
Change in HDL-C level (mg/dL)	-0.5	1.5	0.7969
Change in LDL-C level (mg/dL)	8.0	-1.5	0.1807
Change in VLDL-C level (mg/dL)	-11.5	-1.0	0.0287
Change in Apo-A1 level (g/L)	-0.050	0.015	0.2368
Change in Apo-B level (g/L)	-0.015	0.000	0.8948
Change in Lp(a) level (g/L)	0.000	0.000	0.8163

^a P-values were computed using nonparametric Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Safety Results: Comparable numbers of subjects in each treatment group had treatment-emergent AEs (5 subjects with 5 AEs in the K85 4-g treatment group and 6 subjects with 8 AEs in the placebo treatment group). All treatment-emergent AEs were considered mild-to-moderate in intensity.</p> <p>No subjects died or had any treatment-emergent SAEs during this study. One subject in the K85 4-g treatment group discontinued the study due to a treatment-emergent AE of rheumatoid arthritis.</p> <p>Twelve subjects had shifts from baseline from a lower toxicity grade to a higher toxicity grade (5 subjects with 5 shifts in the K85 4-g treatment group and 7 subjects with 11 shifts in the placebo treatment group). In the K85 4-g treatment group, 5 subjects had 5 shifts from grade 0 to grade 1. In the placebo treatment group, 7 subjects had 10 shifts from grade 0 to grade 1, and 1 subject had a shift from grade 1 to grade 2. No associated AEs were reported for these subjects. No subject had any shift from baseline to a toxicity grade greater than 2.</p>		
<p>Conclusions: Compared with subjects in the placebo, subjects in the K85 4-g treatment group had significantly larger absolute and relative reductions in serum TG, and correspondingly, also had significantly larger absolute and relative reductions in VLDL-C.</p> <p>During this study, K85 4 g per day was considered safe and well tolerated.</p> <p>Date of the report: April 11, 2003</p>		

Appears This Way
On Original

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Title of Study: A Double Blind Study Comparing Treatment with K85 and Placebo (Corn Oil) in Patients with Hyperlipidemia		
Principal Investigators: Dennis Nilsen, MD, PhD		
Study Centers: Rogaland Central Hospital (Stavanger, Norway)		
Publication (reference): Grundt H, Nilsen DW, Hetland O, Aarsland T, Baksaas I, Grande T, et al. Improvement of serum lipids and blood pressure during intervention with n-3 fatty acids was not associated with changes in insulin levels in subjects with combined hyperlipidaemia. J Intern Med 1995 Mar; 237(3):249-59.		
Studied period (years): 8 months First subject enrolled: November 22, 1991 Last subject completed: July 29, 1992	Phase of development: Phase III	
Objectives: This trial was designed to investigate the effect of K85 4 g per day in subjects with hyperlipidemia. One protocol-specified objective was to compare the effect of K85 4 g per day with placebo (corn oil) on serum lipid concentrations of TG, TC and HDL-C in subjects who after treatment with a therapeutic diet suffer from hyperlipidemia. A second protocol-specified objective was to compare the tolerability of K85 4 g per day with placebo (corn oil) in subjects with hyperlipidemia.		
Methodology: This study was a randomized, double-blind, parallel-group, placebo-controlled, single-center study of K85 administered orally to subjects with hyperlipidemia. Subjects underwent a 10-week Dietary Run-In Period, in which they were asked to follow the European Atherosclerosis Society lipid-lowering diet, followed by a 12-week Treatment Period with either K85 4 g per day or placebo (corn oil) capsules.		
Number of subjects (planned and analyzed): The planned sample size was 60 subjects with 30 subjects in each treatment arm. The actual sample size was 57 subjects. These subjects were randomly assigned to receive either K85 4 g per day or placebo (corn oil) based on a computer-generated randomization scheme. Of the 57 subjects who were randomized, 28 were in the K85 4-g treatment group and 29 were in the placebo treatment group. All subjects randomized during this study were included in the intent-to-treat (ITT) analysis except for 1 subject in the placebo treatment group who was withdrawn from the study for other reasons. The corresponding per-protocol (PP) population consisted of 28 subjects in the K85 4-g treatment group and 28 subjects in the placebo treatment group.		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Diagnosis and main criteria for inclusion or exclusion: Male or female subjects were included in this study if they were between 18 and 65 years of age; if they had a history of hyperlipidemia and were receiving medication for this condition, but in the opinion of the investigator, could have their medication withdrawn for the duration of the study, or they had hyperlipidemia despite dietary therapy, or they had newly diagnosed hyperlipidemia; if they had mean fasting serum TG levels between 177 and 1326 mg/dL (inclusive) and mean fasting TC levels of at least 232 mg/dL during the final 2 visits of the Dietary Run-In Period; if fasting serum TG values did not differ by more than 50% during the final 2 visits of the Dietary Run-In Period; if they had received treatment with a therapeutic diet for at least 10 weeks; if they had a mean change in body weight of less than 2.2 lb per week during the Dietary Run-In Period; and if they provided written informed consent. Subjects were excluded from this study if they had diabetes mellitus (defined as fasting blood glucose level higher than 126 mg/dL); if they received any dietary supplementation or medication containing omega-3 fatty acids (fish oil concentrates, cod liver oil, or fish flour) during the Dietary Run-In Period; if they had a myocardial infarction or other serious illness within 3 months prior to screening; if they had a severe concurrent illness (including serious psychiatric disease); if they abused alcohol or drugs; if they had been advised to consume fewer than 1500 kcal per day; or if they were pregnant, subjects were of childbearing age but were not using active contraceptive precautions, or subjects were lactating mothers.</p>		
<p>Test product, dose and mode of administration, lot number: Subjects assigned to the K85 treatment arm received four 1-g capsules of K85 daily, administered orally as either one 4-g dose or as two 2-g doses. Lot number 26845 with an expiration date of April 1992 was used for this study.</p>		
<p>Reference therapy, dose and mode of administration, lot number: Subjects assigned to the placebo arm received four 1-g capsules of corn oil daily, administered orally as either one 4-g dose or two 2-g doses. Lot number 26846 with an expiration date of April 1992 was used for this study.</p>		
<p>Criteria for evaluation: Efficacy: The primary efficacy endpoint was the change from baseline to end of study in serum TG levels. Secondary efficacy endpoints included changes from baseline to end of study in TC, HDL-C, low-density lipoprotein cholesterol (LDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), and lipoprotein (a) (Lp[a]) levels.</p>		
<p>Safety: Safety was assessed through the monitoring of adverse events (AEs), serious adverse events (SAEs), concomitant medications, vital signs, body weight, and laboratory assessments.</p>		
<p>Statistical methods: Data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. Primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analyses, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Wilcoxon two-sample test was used to compare median changes and median percentage changes between treatment groups. All statistical tests of significance were 2-tailed with a 5% significance level.</p>		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>	
			Name of Finished Product: K85
			Name of Active Ingredients: EPA and DHA

Summary--Conclusions

Efficacy Results: Efficacy results for the PP population are presented in the tables below:

Summary of Efficacy Results, Relative Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4 g (N = 28) (Median, %)	Placebo (N = 28) (Median, %)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level	-31.3	-7.3	<0.0001
Secondary Efficacy Endpoints			
Change in TC level	-8.9	-5.9	0.8827
Change in HDL-C level	0.0	8.8	0.4837
Change in LDL-C level	-5.5	-10.5	0.1180
Change in Apo-A1 level	-0.403	2.594	0.3545
Change in Apo-B level	-0.510	-2.876	0.4559
Change in Lp(a) level	0.000	2.778	0.4794

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Summary of Efficacy Results, Absolute Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4 g (N = 28) (Median)	Placebo (N = 28) (Median)	P-value ^a
Primary Efficacy Endpoint			
Change in serum TG level (mg/dL)	-84.0	-24.5	<0.0001
Secondary Efficacy Endpoints			
Change in TC level (mg/dL)	-25.5	-15.5	0.7741
Change in HDL-C level (mg/dL)	0.0	4.0	0.2685
Change in LDL-C level (mg/dL)	-10.0	-16.5	0.2283
Change in Apo-A1 level (g/L)	-0.005	0.040	0.3214
Change in Apo-B level (g/L)	-0.010	-0.050	0.4314
Change in Lp(a) level (g/L)	0.000	0.010	0.2203

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Safety Results: Comparable numbers of subjects in each treatment group had treatment-emergent AEs (12 subjects with 19 AEs in the K85 4-g treatment group and 9 subjects with 15 AEs in the placebo treatment group). The majority of these AEs were considered mild-to-moderate in intensity. No more than 1 subject in either treatment group had any single treatment-emergent AE that was considered severe in intensity. Additionally, comparable numbers of subjects in each treatment group had treatment-emergent AEs that were considered related to study drug (6 subjects with 9 AEs in the K85 4-g treatment group and 7 subjects with 12 AEs in the placebo treatment group).</p> <p>No subjects died, had any treatment-emergent SAEs, or discontinued due to a treatment-emergent AE.</p> <p>Sixteen subjects (7 subjects in the K85 4-g treatment group and 9 subjects in the placebo treatment group) had 19 shifts from baseline from a lower toxicity grade to a higher toxicity grade. In the K85 4-g treatment group, 6 subjects had 8 shifts from grade 0 to grade 1, and 1 subject had a shift from grade 1 to grade 2. In the placebo treatment group, 8 subjects had 9 shifts from grade 0 to grade 1, and 1 subject had 1 shift from grade 0 to high range. No associated AEs were reported for these subjects.</p> <p>No subject had any shift from baseline to a toxicity grade greater than grade 2.</p>		
<p>Conclusions: Compared with subjects in the placebo treatment group, subjects in the K85 4-g treatment group had significantly larger absolute and relative reductions in serum TG.</p> <p>During this study, K85 4 g per day was considered safe and well tolerated.</p> <p>Date of the report: April 11, 2003</p>		

Appears This Way
On Original

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Title of Study: A Double-blind Study Comparing Omacor™ (K85) and Placebo in Patients with Type IIb Hyperlipidemia Treated with Simvastatin		
Principal Investigators: Paul N Durrington, MD; Deepak Bhatnagar, MD		
Study centers: Manchester Royal Infirmary, University of Manchester, Manchester, UK (Durrington); Royal Oldham Hospital, Oldham, UK (Bhatnagar)		
Publication (reference): Durrington PN, Bhatnagar D, Mackness MI, Morgan J, Julier K, Khan MA, et al. An omega-3 polyunsaturated fatty acid concentrate administered for one year decreased triglycerides in simvastatin treated patients with coronary heart disease and persisting hypertriglyceridaemia. Heart 2001;85:544-48.		
Studied period: 28 months First subject randomized: March 5, 1996 Last subject completed: July 1, 1998	Phase of development: Phase III	
Objectives: This trial was designed to investigate the effect of K85 4 g per day in subjects with established coronary heart disease (CHD) and investigator-defined Type IIb hyperlipidemia who received concomitant treatment with simvastatin. The protocol-specified primary objective was to compare the change in serum triglyceride (TG) levels between subjects treated with K85 4 g per day and simvastatin and subjects treated with placebo (corn oil) and simvastatin. The protocol-specified secondary objectives were to compare the changes in total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C), very-low-density lipoprotein cholesterol (VLDL-C), apolipoprotein A1 (Apo-A1), apolipoprotein B (Apo-B), lipoprotein(a) (Lp[a]), and fibrinogen levels, and the changes in blood pressure between subjects treated with K85 4 g per day and simvastatin and subjects treated with placebo (corn oil) and simvastatin.		
Methodology: This study was a multicenter, randomized, double-blind, parallel-group, placebo-controlled study of K85 4 g per day administered orally to subjects with CHD and investigator-defined Type IIb hyperlipidemia. Subjects underwent a 6-week Dietary Run-In Period in which they were treated with simvastatin once each evening for 6 weeks and were asked to follow lipid-lowering diet recommendations, followed by a 24-week Double-blind Period with either K85 4 g per day with simvastatin or placebo (corn oil) capsules with simvastatin. After completing the Double-blind Period, all subjects were given the option of participating in a 24-week extension study (Extension Period). Subjects who participated in the extension study received K85 4 g per day and simvastatin.		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Number of subjects (planned and analyzed): The planned sample size was 54 subjects with approximately 27 subjects in each treatment arm. The actual sample size was 59 subjects. These subjects were randomly assigned to receive either K85 4 g per day and simvastatin or placebo (corn oil) and simvastatin based on a computer-generated randomization scheme.		
During the Double-blind Period, 30 subjects were randomized to receive K85 4 g per day with concurrent simvastatin (K85 4-g treatment group) and 29 subjects were randomized to receive placebo with concurrent simvastatin (placebo treatment group). All subjects randomized to the K85 4-g treatment group were included in the ITT population for the Double-blind Period. Two subjects randomized to the placebo treatment group did not have at least 1 postbaseline assessment and were not included in the ITT population. The corresponding ITT population for the Double-blind period consisted of 30 subjects in the K85 4-g treatment group and 27 subjects in the placebo treatment group. One subject in the K85 4-g treatment group and 3 subjects in the placebo treatment group were withdrawn from the study. Five subjects in the K85 4-g treatment group and 8 subjects in the placebo treatment group were excluded from the PP population since they did not have the protocol-specified average TG assessment at the end of the Double-blind Period. The corresponding PP population for the Double-blind period consisted of 25 subjects in the K85 4-g treatment group and 21 subjects in the placebo treatment group.		
During the Extension Period, 46 subjects (25 subjects in the K85 4-g/K85 4-g treatment group and 21 subjects in the placebo/K85 4-g treatment group) received K85 4 g per day and concurrent simvastatin. All subjects who entered the Extension Period were included in the ITT population for that treatment period. One subject in the placebo/K85 4-g treatment group was excluded from the PP population since the subject did not have the protocol-specified single TG assessment at the end of the Extension Period.		
Diagnosis and main criteria for inclusion or exclusion: Male subjects were included in this study if they were between 18 and 75 years of age and female subjects were included in this study if they were less than 75 years of age and were postmenopausal or had had a hysterectomy and had stable estrogen therapy; if they had established CHD and Type IIb hyperlipidemia with mean serum TG levels at least 204 mg/dL; and if they signed the informed consent form (ICF). Subjects were excluded from this study if they had been treated with lipid-lowering drugs other than simvastatin less than 6 weeks before randomization; if they had type 1 diabetes mellitus; if they had a myocardial infarction within 6 months of entering the study; if they were known to be suffering from any disease or taking any medication other than beta-blocker drugs that could affect lipoprotein metabolism; if their Data Sheets revealed a contraindication to simvastatin; if they had received previous treatment with probucol; or if they had unstable body weights.		
Test product, dose and mode of administration, lot number: Subjects assigned to the K85 treatment arm received four 1-g capsules of K85 daily. Lot numbers 56746 and 61027 with expiration dates of December 1996 and September 1998, respectively, were used for this study.		
Reference therapy, dose and mode of administration, lot number: Subjects assigned to the placebo arm received four 1-g capsules of corn oil daily. Lot numbers 49964 and 59110 with expiration dates of December 1996 and September 1998, respectively, were used for this study.		
Criteria for evaluation: Efficacy: The primary efficacy endpoint was the change from baseline to end of treatment period in serum TG levels. Secondary efficacy endpoints included changes from baseline to end of treatment period in TC, HDL-C, LDL-C, VLDL-C, Apo-AI, Apo-B, and Lp(a) levels.		
Safety: Safety was assessed through the monitoring of treatment-emergent adverse events (AEs), treatment-emergent serious adverse events (SAEs), concomitant medications, blood pressure, body weight, laboratory assessments, and physical examination results.		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>	
Name of Finished Product: K85			
Name of Active Ingredients: EPA and DHA			
Statistical methods: Data from both treatment periods were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. For the Double-blind Period, primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analysis, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Wilcoxon two-sample test was used to compare median changes and median percentage changes between treatment groups. All statistical tests of significance were 2-tailed with a 5% significance level.			
Summary–Conclusions			
Efficacy Results: Efficacy results for the PP population in the Double-blind Period are presented in the tables below.			
<p style="text-align: center;">Summary of Efficacy Results, Relative Changes (Per-Protocol Population in Double-blind Period)</p>			
Efficacy Endpoint	K85 4 g (N = 25) (Median, %)	Placebo (N = 21) (Median, %)	P-value^b
Primary Efficacy Endpoint			
Change in serum TG level	-28.9	0.0	0.0012
Secondary Efficacy Endpoints			
Change in TC level	-3.1	1.8	0.0382
Change in HDL-C level	0.0	8.8	0.0425
Change in LDL-C level	0.0	8.1	0.7491
Change in VLDL-C level	-47.8	-26.7	0.1098
Change in Apo-A1 level	-2.885	2.326	0.0148
Change in Apo-B level	-1.980	1.439	0.0392
Change in Lp(a) level	24.329	0.000	0.0718
^a Subjects were treated concomitantly with simvastatin.			
^b Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.			
<p style="text-align: center;">Summary of Efficacy Results, Absolute Changes (Per-Protocol Population in Double-blind Period)</p>			
Efficacy Endpoint	K85 4 g (N = 25) (Median)	Placebo (N = 21) (Median)	P-value^b
Primary Efficacy Endpoint			
Change in serum TG level	-103.0	0.0	0.0017
Secondary Efficacy Endpoints			
Change in TC level (mg/dL)	-7.0	5.0	0.0578
Change in HDL-C level (mg/dL)	0.0	4.0	0.0622
Change in LDL-C level (mg/dL)	0.0	9.0	0.6914
Change in VLDL-C level (mg/dL)	-22.0	-6.0	0.0127
Change in Apo-A1 level (g/L)	-0.030	0.020	0.0181
Change in Apo-B level (g/L)	-0.020	0.020	0.0739
Change in Lp(a) level (g/L)	0.055	0.000	0.0229
^a Subjects were treated concomitantly with simvastatin.			
^b Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.			

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		

Efficacy results for the ITT population in the Extension Period are presented in the tables below.

Summary of Efficacy Results, Relative Changes (ITT Population in Extension Period)

Efficacy Endpoint	K85 4 g/K85 4 g ^a (N = 25) (Median, %)	Placebo/K85 4 g ^a (N = 21) (Median, %)
Primary Efficacy Endpoint		
Change in serum TG level	-5.2	-26.6
Secondary Efficacy Endpoints		
Change in TC level	-1.1	-6.8
Change in HDL-C level	21.4	0.0
Change in LDL-C level	-22.4	-9.0
Change in VLDL-C level	1.7	-31.6
Change in Apo-A1 level	8.911	-0.521
Change in Apo-B level	0.000	-2.834
Change in Lp(a) level	16.310	-4.225

^a Subjects were treated concomitantly with simvastatin.

Summary of Efficacy Results, Absolute Changes (ITT Population in Extension Period)

Efficacy Endpoint	K85 4 g/K85 4 g ^a (N = 25) (Median)	Placebo/K85 4 g ^a (N = 21) (Median)
Primary Efficacy Endpoint		
Change in serum TG level	-20.0	-81.0
Secondary Efficacy Endpoints		
Change in TC level (mg/dL)	-2.0	-17.0
Change in HDL-C level (mg/dL)	9.0	0.0
Change in LDL-C level (mg/dL)	-25.0	-14.0
Change in VLDL-C level (mg/dL)	0.5	-6.0
Change in Apo-A1 level (g/L)	0.080	-0.005
Change in Apo-B level (g/L)	0.000	-0.035
Change in Lp(a) level (g/L)	0.045	-0.020

^a Subjects were treated concomitantly with simvastatin.

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Safety Results: During the Double-blind Period (when subjects received either K85 4-g per day with simvastatin or placebo with simvastatin), more subjects in the K85 4-g treatment group had treatment-emergent AEs (20 subjects with 38 AEs) compared to subjects in the placebo treatment group (14 subjects with 30 AEs). Of particular note, 5 subjects in the K85 4-g treatment group had angina pectoris compared to no subjects in the placebo treatment group; however, 1 subject in the placebo treatment group died due to a myocardial infarction. The majority of treatment-emergent AEs were considered mild-to-moderate in intensity. One subject in the K85 4-g treatment group and 3 subjects in the placebo treatment group had treatment-emergent AEs for which the intensity was not recorded on the CRF. Additionally, all treatment-emergent AEs were considered related to study drug.</p> <p>During the Extension Period (when all subjects received K85 4 g per day), 11 subjects experienced 17 treatment-emergent AEs). The majority of treatment-emergent AEs were considered mild-to-moderate in intensity. Two subjects in the placebo/K85 4-g treatment group had treatment-emergent AEs for which the intensity was not recorded on the CRF. Additionally, all treatment-emergent AEs were considered related to study drug.</p> <p>During the Double-blind Period, 3 subjects in the K85 4-g treatment group and 2 subjects in the placebo treatment group had treatment-emergent SAEs. These SAEs were considered moderate to severe and related to study drug. One subject each in the K85 4-g and placebo groups discontinued the study due to treatment-emergent AEs. One subject in the placebo treatment group died during the Double-blind Period due to a myocardial infarction. The myocardial infarction was considered severe and related to study drug.</p> <p>During the Extension Period, 1 subject experienced a treatment-emergent SAE. No subjects died or discontinued the study due to a treatment-emergent AE.</p> <p>During the Double-blind Period, 13 subjects (7 subjects in the K85 4-g treatment group and 6 subjects in the placebo treatment group) had shifts from baseline from a lower toxicity grade to a higher toxicity grade. In the K85 4-g treatment group, 6 subjects had 8 shifts from grade 0 to grade 1, and 1 subject had a shift from grade 0 to grade 2. In the placebo treatment group, 6 subjects had 7 shifts from grade 0 to grade 1. No associated AEs were reported for these subjects.</p> <p>During the Extension Period, 14 subjects (7 subjects in the K85 4-g/ K85 4-g treatment group and 7 subjects in the placebo/ K85 4-g treatment group) had shifts from baseline from a lower toxicity grade to a higher toxicity grade. In the K85 4-g/ K85 4-g treatment group, 6 subjects had 7 shifts from grade 0 to grade 1, and 1 subject had a shift from grade 1 to grade 2. In the placebo treatment group, 6 subjects had 6 shifts from grade 0 to grade 1 and 1 subject had a shift from grade 0 to high. No associated AEs were reported for these subjects.</p> <p>No subject had a shift from baseline in any laboratory parameter to a toxicity grade greater than grade 2.</p>		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Conclusions: Results from the Double-blind and Extension Periods demonstrate that treatment with K85 4 g per day with simvastatin is associated with significantly larger reductions in TG levels compared to treatment with simvastatin alone.</p> <p>During the Double-blind Period (when subjects received either K85 4-g per day with simvastatin or placebo treatment with simvastatin), subjects in the K85 4-g treatment group had significantly larger absolute and relative reductions in serum TG levels compared to subjects in the placebo treatment group, and correspondingly, also had significantly larger absolute reductions in VLDL-C levels. Relative changes in TC and HDL-C levels were also significantly different between treatment groups. Additionally, subjects in the K85 4-g treatment group had significantly different absolute and relative changes in Apo-A1 levels, relative changes in Apo-B levels, and absolute changes in Lp(a) levels. Absolute and relative changes in LDL-C levels; absolute changes in TC and Apo-B levels; and relative changes in VLDL-C and Lp(a) levels were not significantly different between treatment groups.</p> <p>Although results were not statistically analyzed, during the Extension Period (when all subjects received K85 4 g per day with simvastatin), median relative and absolute changes in TG levels appeared to be minimal for subjects in the K85 4-g/K85 4-g treatment group. Subjects in the placebo/K85 4-g treatment group appeared to have had median relative and absolute reductions in TG. However, these results are based on single TG measurements and should be interpreted cautiously. Subjects in the K85 4-g/K85 4-g treatment group appeared to have had median relative and absolute reductions in LDL-C levels, while median changes in LDL-C levels appeared to be minimal for subjects in the placebo/K85 4-g treatment group. Additionally, subjects in the K85 4-g/K85 4-g treatment group appeared to have had median relative and absolute increases in HDL-C levels, while median changes in HDL-C levels appeared to be minimal in subjects in the placebo/K85 4-g treatment group. Median relative and absolute changes in VLDL-C appeared to be minimal for subjects in the K85 4-g/K85 4-g treatment group, while subjects in the placebo/K85 4-g treatment group appeared to have had median relative and absolute reductions in VLDL-C levels. Subjects in the K85 4-g/K85 4-g treatment group appeared to have had median relative and absolute increases in Lp(a) levels, while median relative and absolute changes in Lp(a) levels appeared to be minimal for subjects in the placebo/K85 4-g treatment group. Median relative and absolute changes in TC, Apo-A1, and Apo-B levels appeared to be minimal for both treatment groups.</p> <p>During this study, concurrent treatment with K85 4 g per day and simvastatin was considered safe and well tolerated</p> <p>Date of the report: April 11, 2003</p>		

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part Of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85 Name of Active Ingredients: EPA and DHA		
Title of Study: A Double Blind Study of Omacor™ (K85) and Lopid® in Subjects with Severe Hypertriglyceridemia		
Principal Investigators: JJP Kastelein, MD, PhD; AFH Stalenhoef, MD, PhD		
Study center(s): Academic Medical Center, Amsterdam, Netherlands, and Slotervaart Hospital, Amsterdam, Netherlands (Kastelein); University Hospital Nijmegen, Nijmegen, Netherlands (Stalenhoef)		
Publication (reference): Stalenhoef AF, de Graaf J, Wittekoek ME, Bredie SJ, Demacker PN, Kastelein JJ. The effect of concentrated n-3 fatty acids versus gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertriglyceridemia. <i>Atherosclerosis</i> 2000;153(1):129-38.		
Studied period (years): 1.6 years First subject randomized: August 1, 1995 Last subject completed: March 6, 1997	Phase of development: Phase III	
<p>Objectives: This trial was designed to compare the effect of K85 4 g per day with gemfibrozil 1200 mg per day in subjects with severe hypertriglyceridemia (HTG).</p> <p>The protocol-specified primary objective was to compare the change in serum triglyceride (TG) levels between subjects treated with K85 4 g per day and subjects treated with gemfibrozil 1200 mg per day.</p> <p>The protocol-specified secondary objectives were to compare the changes in total cholesterol (TC); high-density lipoprotein cholesterol (HDL-C); very-low-density lipoprotein cholesterol (VLDL-C); apolipoproteins A1 (Apo-A1), B (Apo-B), and E (Apo-E); lipoproteins aI (Lp[a]I) and aII (Lp[a]II); free fatty acids (FFAs); and vitamin E.</p> <p>An additional protocol-specified objective was to measure the oxidizability of low-density lipoprotein (LDL), LDL size, content of fatty acids, and vitamin E levels between subjects treated with K85 4 g per day and subjects treated with gemfibrozil 1200 mg per day in a random subgroup of 30 subjects.</p>		
<p>Methodology: This study was a multicenter, randomized, double-blind, parallel-group, comparator-controlled study of K85 4 g per day administered orally to subjects with severe HTG. Subjects underwent a 6-week Dietary Run-In Period, in which they were asked to follow the National Guidelines for Healthy Nutrition in the Netherlands, followed by a 12-week Treatment Period with either K85 4 g per day capsules or gemfibrozil 1200 mg per day tablets. Subjects randomized to the K85 4-g treatment group received 4 capsules of K85 and 2 tablets of gemfibrozil placebo daily. Subjects randomized to the gemfibrozil treatment group received 4 capsules of K85 placebo (corn oil) and 2 tablets of gemfibrozil daily.</p>		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part Of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Number of subjects (planned and analyzed): The planned sample size was 100 subjects with approximately 50 subjects in each treatment arm. The actual sample size was 98 subjects. These subjects were randomly assigned to receive either K85 4 g per day or gemfibrozil 1200 mg per day based on a computer-generated randomization scheme.</p> <p>Of the 98 subjects who were randomized, 49 subjects received K85 4 g per day and 49 subjects received gemfibrozil 1200 mg per day. The intent-to-treat (ITT) population consisted of 48 subjects in the K85 4-g treatment group and 49 subjects in the gemfibrozil treatment group. Three subjects in the K85 4-g treatment group and 3 subjects in the gemfibrozil treatment group were withdrawn due to treatment-emergent adverse events (AEs), 1 subject in the gemfibrozil treatment group was withdrawn due to refusal, and 1 subject in each treatment group was withdrawn for other reasons. The per-protocol (PP) population consisted of 41 subjects in the K85 4-g treatment group and 42 subjects in the gemfibrozil treatment group.</p>		
<p>Diagnosis and main criteria for inclusion or exclusion: Male or female were included in this study if they were between 18 and 70 years of age; if they had had severe HTG; if they had mean serum TG levels greater than 398.6 mg/dL at Weeks -6 and -2; (Visits -2 and -1) and if they signed the informed consent form (ICF). Subjects were excluded from this study if they received treatment with fibric acid derivatives (FADs) within 6 weeks of entering the study; if they received treatment with cod liver oil, other omega-3 fatty acid products, or lipid-lowering fibers within 4 weeks of entering the study; if they were pregnant or lactating mothers; if they exhibited excessive use of alcohol (more than 2 drinks per day), abused drugs, or had any condition associated with a risk of poor compliance; if they had a myocardial infarction or other serious illness within 6 months of entering the study; if they had clinically significant disease as judged by the investigator; if they had asthma; or if they had hypersensitivity to acetylsalicylic acid.</p>		
<p>Test product, dose and mode of administration, lot number: Subjects assigned to the K85 4-g treatment group received four 1-g capsules of K85 daily, administered orally as two 2-g doses. Lot number 47586 with an expiration date of June 1996 was used for this study.</p>		
<p>Test product placebo control, dose and mode of administration, lot number: Subjects assigned to the K85 4-g treatment group received two 600-mg tablets of gemfibrozil placebo daily, administered orally as two 600-mg doses. Lot number 0230494 with an expiration date of May 1997 was used for this study.</p>		
<p>Reference therapy, dose and mode of administration, lot number: Subjects assigned to the gemfibrozil treatment group received two 600-mg tablets of gemfibrozil daily, administered orally as two 600 mg doses. Lot number 0309064-CG with an expiration date of May 1997 was used for this study.</p>		
<p>Reference therapy placebo control, dose and mode of administration, lot number: Subjects assigned to the gemfibrozil treatment group received four 1-g capsules of K85 placebo (corn oil) daily, administered orally as two 2-g doses. Lot number 49964 with an expiration date of June 1996 was used for this study.</p>		
<p>Criteria for evaluation: Efficacy: The primary efficacy endpoint was the change from baseline to end of study in serum TG levels. Secondary efficacy endpoints included changes from baseline to end of study in the levels of TC, HDL-C, LDL-C, VLDL-C, Apo-A1, Apo-B, Lp(a)I, and Lp(a)II levels.</p>		
<p>Safety: Safety was assessed through the monitoring of treatment-emergent AEs, treatment-emergent serious adverse events (SAEs), concomitant medications, blood pressure, body weight, body mass index (BMI), laboratory assessments, and physical examinations.</p>		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part Of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>	
Name of Finished Product: K85			
Name of Active Ingredients: EPA and DHA			
<p>Statistical methods: Data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. Primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analysis, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Wilcoxon two-sample test was used to compare median changes and median percentage changes between treatment groups. All statistical tests of significance were 2-tailed with a 5% significance level.</p>			
Summary–Conclusions			
Efficacy Results: Efficacy results for the PP population are presented in the tables below:			
Summary of Efficacy Results, Relative Changes (Per-Protocol Population)			
Efficacy Endpoint	K85 4 g (N = 41) (Median, %)	Gemfibrozil (N = 42) (Median, %)	P-value^a
Primary Efficacy Endpoint			
Change in serum TG level	-35.8	-60.0	0.0002
Secondary Efficacy Endpoints			
Change in TC level	-7.5	-12.0	0.2949
Change in HDL-C level	2.9	19.9	0.0012
Change in LDL-C level	6.6	1.9	0.8529
Change in VLDL-C level	-26.1	-28.3	0.5475
Change in Apo-A1 level	-1.411	1.194	0.3241
Change in Apo-B level	11.977	11.454	0.9944
Change in Lp(a)I level	-3.943	-11.364	0.0822
Change in Lp(a)II level	0.000	19.444	0.7004
^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.			
Summary of Efficacy Results, Absolute Changes (Per-Protocol Population)			
Efficacy Endpoint	K85 4 g (N = 41) (Median)	Gemfibrozil (N = 42) (Median)	P-value^a
Primary Efficacy Endpoint			
Change in serum TG level (mg/dL)	-256.0	-369.5	0.1621
Secondary Efficacy Endpoints			
Change in TC level (mg/dL)	-27.0	-35.0	0.4306
Change in HDL-C level (mg/dL)	1.0	5.0	0.0006
Change in LDL-C level (mg/dL)	8.0	3.0	0.7245
Change in VLDL-C level (mg/dL)	-27.0	-31.0	0.7544
Change in Apo-A1 level (g/L)	-0.020	0.015	0.2938
Change in Apo-B level (g/L)	0.185	0.185	0.8824
Change in Lp(a)I level (g/L)	-0.035	-0.080	0.1236
Change in Lp(a)II level (g/L)	0.000	0.140	0.3324
^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.			

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part Of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Safety Results: Fewer subjects in the K85 4-g treatment group than in the gemfibrozil treatment group had treatment-emergent AEs (7 subjects with 9 AEs in the K85 4-g treatment group and 11 subjects with 20 AEs in the gemfibrozil treatment group). The majority of treatment-emergent AEs were considered mild-to-moderate in intensity. All treatment-emergent AEs were considered related to study drug.</p> <p>One subject in the gemfibrozil treatment group died during the study due to severe myocardial infarction. One subject in the K85 4-g treatment group had 1 treatment-emergent SAE (pancreatitis), and 3 subjects in the gemfibrozil treatment group each had 1 treatment-emergent SAE (angina pectoris, myocardial infarct, and hypoglycemic reaction). All treatment-emergent SAEs were considered moderate-to-severe in intensity and related to study drug. Three subjects in the K85 4-g treatment group and 3 subjects in the gemfibrozil treatment group discontinued the study due to treatment-emergent AEs.</p> <p>No subject had a shift from baseline in any laboratory parameter to a toxicity grade greater than grade 1.</p>		
<p>Conclusions: Compared with subjects in the K85 4-g treatment group, subjects in the gemfibrozil treatment group had significantly larger relative reductions in serum TG. Also, subjects in the gemfibrozil treatment group had significantly larger absolute and relative increases in HDL-C compared with subjects in the K85 4-g treatment group.</p> <p>During this study, K85 4 g per day was considered safe and well tolerated.</p> <p>Date of the report: April 11, 2003</p>		

**Appears This Way
On Original**

2. SYNOPSIS

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Title of Study: The Effect of Omacor™ (K85) on Postprandial Lipoprotein Metabolism in Patients with Hypertriglyceridemia		
Principal Investigator: Claus Luley, MD		
Study center(s): Otto-von-Guericke-Universität Magdeburg, Magdeburg, Germany		
Publication (reference): Westphal S, Orth M, Ambrosch A, Osmundsen K, Luley C. Postprandial chylomicrons and VLDLs in severe hypertriacylglycerolemia are lowered more effectively than are chylomicron remnants after treatment with n-3 fatty acids. Am J Clin Nutr 2000;71(4):914-20.		
Studied period (years): 1.1 years First subject randomized: April 5, 1995 Last subject completed: May 14, 1996	Phase of development: Phase III	
<p>Objectives: The protocol-specified primary objective was to compare the effect of K85 4 g per day with placebo (corn oil) on 3 lipoproteins (chylomicrons, chylomicron remnants, and VLDL-C), at regular time intervals for 8 hours after a standardized oral fat load, using elution curves after gel filtration.</p> <p>The protocol-specified secondary objectives were to compare the effects of K85 4 g per day and placebo on serum TG, TC, VLDL-C, LDL-C, and HDL-C levels as separated by preparative ultracentrifugation. Additionally, Apo-A1, Apo-A2, Apo-B, Apo-C3, and Apo-E, LPL, CETP, and FFA levels were determined.</p> <p>While the protocol-specified objectives were as described above, this report focuses on the analyses of serum TG and other lipids. The results of the protocol-specified primary objectives are not being reanalyzed as part of this report.</p>		
<p>Methodology: This study was a randomized, double-blind, parallel-group, placebo-controlled study of K85 4 g per day administered orally to subjects with HTG, defined as serum TG levels greater than 300 mg/dL. Subjects were treated with either K85 4 g per day or placebo (corn oil) capsules for 6 weeks.</p>		
<p>Number of subjects (planned and analyzed): The planned sample size was 20 subjects with 12 subjects in the K85 4-g treatment group and 8 subjects in the placebo treatment group. The actual sample size was 21 subjects. These subjects were randomly assigned to receive either K85 4 g per day or placebo (corn oil) based on a computer-generated randomization scheme.</p> <p>Of the 21 subjects who were randomized, 12 received K85 4 g per day and 9 received placebo (corn oil). All subjects randomized during this study were included in the intent-to-treat (ITT) analysis. One subject in the placebo treatment group was withdrawn from the study. The corresponding per-protocol (PP) population consisted of 12 subjects in the K85 4-g treatment group and 8 subjects in the placebo treatment group.</p>		

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
Diagnosis and main criteria for inclusion or exclusion: Male subjects were included in this study if they were between 21 and 65 years of age, if they had fasting TG levels greater than 300 mg/dL at Visit -1, and if they signed the informed consent form (ICF). Subjects were excluded from this study if they had unstable diabetes mellitus; if they received treatment with other lipid-lowering drugs or other omega-3 fatty acid products within 2 months prior to enrollment; if they ate fat (cold-water) fish more than once per week; if they had hyperlipidemia type III; if they had contraindications to K85, such as a known or suspected allergy; if they needed concomitant therapy which may have interfered with the trial drug; or if they abused alcohol (greater than 2 drinks per day) or drugs, or had any condition associated with a risk of poor compliance.		
Test product, dose and mode of administration, lot number: Subjects assigned to the K85 treatment arm received four 1-g capsules of K85 daily, administered orally as one 4-g dose. Lot number 47586 with an expiration date of June 1996 was used for this study.		
Reference therapy, dose and mode of administration, lot number: Subjects assigned to the placebo arm received four 1-g capsules of corn oil daily, administered orally as one 4-g dose. Lot number 49964 with an expiration date of December 1996 was used for this study.		
Criteria for evaluation: Efficacy: The primary efficacy endpoint was the change from baseline to end of study in serum TG levels. Secondary endpoints included changes from baseline to end of study in TC, HDL-C, LDL-C, VLDL-C, Apo-A1, and Apo-B levels.		
Safety: Safety was assessed through the monitoring of treatment-emergent adverse events (AEs), treatment-emergent serious adverse events (SAEs), concomitant medications, vital signs, body weight, and laboratory assessments.		
Statistical methods: Data were summarized using descriptive statistics (number of subjects, mean, median, standard deviation, minimum, and maximum) for continuous variables, and frequencies and percentages for discrete variables. Primary and secondary efficacy outcomes were analyzed using both nonparametric and parametric approaches (primary and supportive analyses, respectively). Analysis of variance (ANOVA) models were used to compare mean changes and mean percentage changes between treatment groups. The Wilcoxon two-sample test was used to compare median changes and median percentage changes between treatment groups. All statistical tests of significance were 2-tailed with a 5% significance level.		

**Appears This Way
On Original**

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier	(For National Authority Use Only)
	Volume: Page:	
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		

Summary–Conclusions

Efficacy Results: Efficacy results for the PP population are presented in the tables below:

Summary of Efficacy Results, Relative Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4 g (N = 12) (Median, %)	Placebo (N = 8) (Median, %)	P-value ^a
TG Efficacy Endpoint			
Change in serum TG level	-29.1	-7.6	0.1770
Other Lipids Efficacy Endpoint			
Change in TC level	-5.4	3.1	0.2976
Change in HDL-C level	-8.7	8.7	0.2774
Change in LDL-C level	39.0	3.7	0.1137
Change in VLDL-C level	-27.6	11.3	0.0078
Change in Apo-A1 level	-2.710	0.460	0.6160
Change in Apo-B level	11.905	-3.577	0.2318

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups.

Summary of Efficacy Results, Absolute Changes (Per-Protocol Population)

Efficacy Endpoint	K85 4 g (N = 12) (Median)	Placebo (N = 8) (Median)	P-value ^a
TG Efficacy Endpoint			
Change in serum TG (mg/dL)	-363.0	-26.5	0.2318
Other Lipids Efficacy Endpoint			
Change in TC level (mg/dL)	-23.5	10.0	0.2160
Change in HDL-C level (mg/dL)	-3.5	2.0	0.2755
Change in LDL-C level (mg/dL)	28.5	5.0	0.0895
Change in VLDL-C level (mg/dL)	-59.5	15.5	0.0252
Change in Apo-A1 level (g/L)	-0.035	-0.000	0.6433
Change in Apo-B level (g/L)	0.110	-0.060	0.2316

^a Nonparametric P-values are presented. Nonparametric P-values were computed using Wilcoxon two-sample tests to evaluate the overall treatment effect.

Safety Results: No subjects had any treatment-emergent AEs or SAEs, and no subjects died during this study.

No subject had a shift from baseline in any laboratory parameter to a toxicity grade greater than 1.

Name of Company: Pronova Biocare a.s	Individual Study Table Referring to Part of the Dossier Volume: Page:	<i>(For National Authority Use Only)</i>
Name of Finished Product: K85		
Name of Active Ingredients: EPA and DHA		
<p>Conclusions: While the protocol-specified primary efficacy endpoint was to compare the effect of K85 4 g per day with placebo on chylomicrons, chylomicron remnants, and VLDL-C, this analysis was not repeated during the Ross reanalyses. In a published manuscript of the original analyses, the following conclusion was reached regarding the protocol-specified primary efficacy endpoint: "n-3 Fatty acids effectively lower chylomicrons and VLDLs, but their effect on chylomicron remnants was observed only in the late postprandial phase."</p> <p>Compared with subjects in the placebo treatment group, subjects in the K85 4-g treatment group did not have significantly different relative and absolute changes in serum TG levels. The statistically insignificant differences in TG are not surprising, given that this study was not powered to detect differences between groups in TG reduction. However, significantly more subjects in the K85 4-g treatment group than in the placebo treatment group had more than a 20% reduction in TG level at the end of the study. Subjects in the K85 4-g treatment group also had significantly different relative and absolute changes in VLDL-C levels compared with subjects in the placebo treatment group.</p> <p>During this study, K85 4 g per day was considered safe and well tolerated.</p> <p>Date of the report: April 11, 2003</p>		

Appears This Way
On Original

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Wei Qiu
10/22/04 11:15:53 AM
BIOPHARMACEUTICS

Hae-Young Ahn
10/22/04 12:32:42 PM
BIOPHARMACEUTICS

**OFFICE OF CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS
REVIEW**

NDA: 21-853	Submission Date(s): Jan 9, 2004; Jan 20, 2004; July 20, 2004; Aug 17, 2004; September 21, 2004
Brand Name	Omacor®
Generic Name	Omega-3-acid ethyl esters
Reviewer	Wei Qiu, Ph.D.
Team Leader	Hae-Young Ahn, Ph.D.
OCPB Division	DPEII
ORM division	Metabolic and Endocrine Drug Products
Sponsor	Ross Products Division, Abbott Laboratories
Relevant IND(s)	45,998
Submission Type	Original
Formulation; Strength(s)	Liquid-filled gel capsules; 1 g
Indication	As an adjunct to diet to reduce triglyceride levels

Table of Contents

1	Executive Summary	1
1.1	Recommendation	2
1.2	Phase IV Commitments	2
1.3	Summary of Important Clinical Pharmacology and Biopharmaceutics Findings	2
2	Question Based Review	4
2.1	General Attributes of the Drug	4
2.2	General Clinical Pharmacology	5
2.3	Intrinsic Factors	8
2.4	Extrinsic Factors	11
2.5	General Biopharmaceutics	12
2.6	Analytical Section	13
3	Detailed Labeling Recommendations	13
4	Appendix	14
4.1	Cover Sheet and OCPB Filing/Review Form	14

1 Executive Summary

Abbott Laboratories, Ross Products Division submitted an NDA for Omacor® (also known as K85) on January 9, 2003, Jan. 20, 2004, July 20, 2004, Aug. 17, 2004, and September 21, 2004. The proposed indication for Omacor® is as an adjunct to diet to reduce triglyceride levels.

The clinical pharmacology section contains study reports or published articles for seven studies in healthy subjects (CK85-001, CK85-002, CK85-006 (article), CK85-007, CK85-027 (article), K85-91003/K85-92006, and K85-99023). One published article of a study conducted in hypertension

patients (CK85-003) and one published article of a study conducted in IgA nephropathy patients (K85-95015) were included. This reviewer requested electronic versions of the data for those studies which had study reports but the sponsor replied that since these studies were completed approximately 15 years ago by Pronova in the UK and Norway, the electronic versions of these data bases were not available. The raw data for study CK85-001 and CK85-002 but not other studies mentioned above were included. The incorporation of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) into blood phospholipids were evaluated.

In one phase II (CK85-013) and 13 phase III trials in subjects with hypertriglyceridemia (CK85-012, CK85-014, CK85-017, CK85-019, CK85-022, CK85-023, K85-92004, K85-94010, K85-94110, K85-95009, K85-95011, K85-95012, and K85-95014), EPA and DHA participation in serum phospholipids were determined. The sponsor provided electronic datasets for these studies.

The sponsor also included an In vitro evaluation of inhibition of P450s using human liver microsomes.

CPB Briefing was held on October 1, 2004.

Attendees: John Hunt, Chandra Sahajwalla, Arzu Selen, Hae-Young Ahn, Mary Parks, and Wei Qiu.

Post briefing meeting with Division Director Dr. Henry Malinowski on Oct. 4, 2004: Since the drug substance is oil which is insoluble in water, it was concluded that disintegration test would be adequate for quality control purpose. The sponsor submitted disintegration data in CMC section and the Chemist reviewer, Dr. Martin Haber found the data acceptable.

1.1 Recommendation

The Office of Clinical Pharmacology and Biopharmaceutics/Division of Pharmaceutical Evaluation 2 (OCPB/DPE-2) has reviewed NDA 21-853 submitted on Jan 9, 2004, Jan 20, 2004, July 20, 2004, Aug 17, 2004 and Sept 21, 2004 and finds it acceptable provided that satisfactory agreement is reached between the sponsor and the Agency regarding the language in the package insert. Recommendation, Phase IV commitments, and labeling comments should be conveyed to the sponsor as appropriate.

1.2 Phase IV Commitments

T

b(4)

└

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

Dose-exposure relationship:

Nonlinear relationship between dose and percentage increase in EPA and DHA in serum phospholipids was demonstrated over the daily dose range of 2 to 8 g in patients with hyperlipidemia. The incorporation of EPA increased as dose increased. However, the

incorporation of DHA was not dose dependent. Omacor treated groups had statistically significant higher EPA and DHA levels than the placebo group (**Figure 1**).

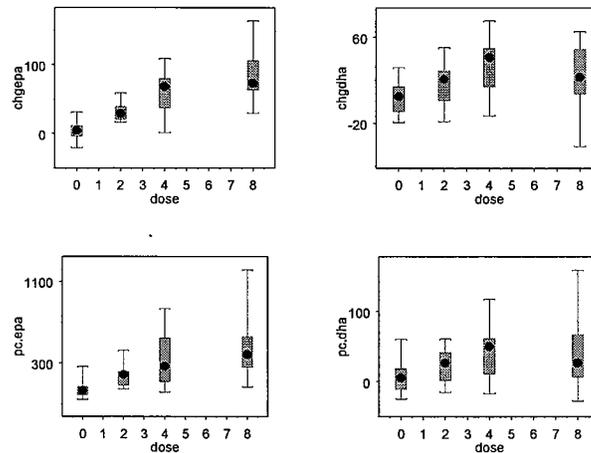


Figure 1. Dose-concentration relationship. Absolute change in EPA (chgepa, upper left panel); percentage change in EPA (pc.epa, lower left panel); absolute change in DHA (chgdha, upper right panel); and percentage change in DHA (pc.dha, lower right panel).

Dose-response relationship:

Dose-response relationship was demonstrated over the daily dose range of 2 to 8 g. There was a trend that as dose increased, triglyceride (TG) tended to decrease. However, the reduction in TG levels were not significantly different between placebo, 2, 4, or 8 g treatment groups due to large variability and small sample size (**Figure 2**). Although the small phase 2 trial showed no effectiveness of Omacor on lowering TG levels, several phase 3 trials demonstrated that 4 g Omacor was effective.

Appears This Way
On Original

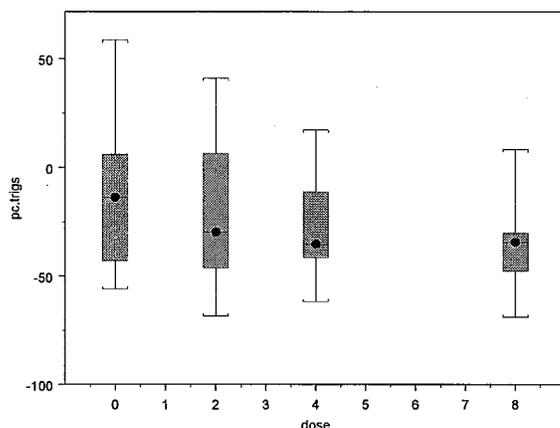


Figure 2. Percentage change in triglyceride (pc.trigs) vs. dose.

2 Question Based Review

2.1 General Attributes of the Drug

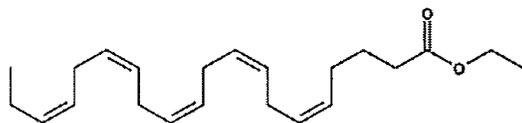
1. What are the highlights of the chemistry and physical-chemical properties of the drug substance?

The drug substance is a purified, _____ mixture of omega-3-acid ethyl esters. The two predominant components of the drug substance are the ethyl esters of eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The primary remaining components of the drug substance are ethyl esters of [_____]

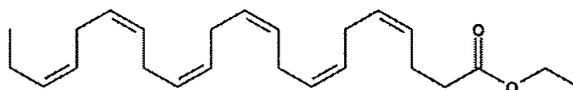
b(4)

_____] The drug substance is practically insoluble in water.

The structural formula of EPA ethyl ester is:



The structural formula of DHA ethyl ester is:



2. What is the formulation of the drug product ?

The drug product is a soft gelatin capsule. Each capsule contains at least 900 mg omega-3-acid ethyl esters. These are predominately comprised of approximately 840 mg of a combination of the ethyl esters of eicosapentaenoic acid (EPA), approximately 465 mg and docosahexaenoic acid (DHA), approximately 375 mg. Four mg α -tocopherol is added as an antioxidant carried by small amount of partially hydrogenated vegetable oils including soybean oil. Gelatin shell contains : _____ gelatin, _____ glycerin, and trace amount of _____

b(4)

2. What are the proposed mechanism(s) of action and therapeutic indication(s)?

The mechanism of action of Omacor is not completely understood. The proposed potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β -oxidation in the liver. Omacor may reduce the synthesis of triglycerides in the liver because EPA and DHA are poor substrates for the enzymes responsible for triglyceride synthesis, and EPA and DHA inhibit esterification of other fatty acids.

The proposed therapeutic indications are as follows: (1). As an adjunct to diet to reduce triglyceride levels in adult patients [] Omacor reduces triglyceride levels [] when used in conjunction with HMG-CoA reductase inhibitors. Omacor has been shown to have an additive effect in triglyceride level reduction when used in conjunction with HMG-CoA reductase inhibitors. []

b(4)

3. What are the proposed dosage(s) and route(s) of administration?

The proposed daily dose of Omacor is 4 g, which may be taken as a single 4-g dose or as two 2-g doses. The route of administration is oral. In most phase 3 trials, subjects received the medication as one 4-g dose or as two 2-g daily doses.

2.2 General Clinical Pharmacology

1. What are the design features of the clinical pharmacology and clinical studies used to support dosing or claims?

Among the three clinical pharmacology studies where soft gelatin capsules were used, doses were 2, 4, 8, and 14 g per day. The duration was 2, 4, and 7-weeks.

In a phase 2 study (CK85-013), doses of 2, 4, and 8 g per day were given for 8 weeks.

In most phase 3 clinical studies, the 4 g daily dose was given. In study CK85-012, a 6 g per day dose was given. In study K85-92004, 2 g and 3 g per day doses were given.

All these studies were used to support 4 g per day dosing.

2. Are the active moieties in the plasma (or other biological fluid) appropriately identified and measured to assess pharmacokinetic parameters and exposure response relationships?

No. According to the sponsor, the free fatty acid levels in blood were too low to be measured. Since meaningful estimates of C_{max}, t_{max}, AUC for the parent drug and its metabolites can not

be provided for the pharmacokinetic analysis of Omacor, the uptake of EPA and DHA in serum phospholipids is used as a marker of absorption.

The rationale for using EPA and DHA uptake as markers for the absorption of the drug is that the fatty acid composition of the serum phospholipids correlates with levels incorporated in membranes (e.g., erythrocyte, monocyte, and thrombocyte membrane). Omega-3 fatty acid composition of erythrocyte and thrombocyte membranes, in turn, correlates with whole body content of these compounds. Analysis of blood phospholipids is, therefore, a way to assess the performance of products intended to increase total body stores of omega-3 fatty acids. The sponsor measured the increase of EPA and DHA in serum phospholipids to investigate the absorption of K85.

3. Exposure-Response

1). What are the characteristics of the exposure-response relationships (dose-response) for efficacy?

The triglyceride levels decreased as dose increased over the dose range of 2 to 8 g per day. However, the overall reductions in TG levels were not significantly different between placebo, 2 g, 4 g, and 8 g treatment groups partially due to large variability and small sample size.

The dose response relationship was evaluated in a Phase 2 study CK85-013. This was a multicenter, randomized, parallel-group, placebo-controlled study of K85 2 g, 4 g, and 8 g per day administered orally to 69 patients with hyperlipidemia. The duration of treatment was 8 weeks. The subjects took study medication (K85 or placebo) as one 2-g, 4-g, or 8-g dose per day or as two equal daily doses. Placebo was a corn oil capsule.

The percentage change in serum triglyceride is shown in **Figure 2** and **Table 1**. It shows that as K85 dose increased, serum triglyceride levels decreased. However, statistical analysis results showed no significant difference among all four treatment groups. The same study also evaluated the incorporation of EPA and DHA. Results showed that mean overall changes in EPA and DHA levels were significantly different between the K85 2 g, 4 g, and 8 g and placebo treatment groups.

Table 1. Mean (SD) percentage change in triglyceride (TG) levels

Treatment	No. of Subjects	Percentage change in TG (%)
Placebo	17	-15.31 ± 29.75
K85 2 g	16	-21.91 ± 31.02
K85 4 g	15	-27.68 ± 20.70
K85 8 g	18	-36.73 ± 17.15

2) Does this drug prolong the QT or QTc interval?

The effect of Omacor on QT/QTc interval prolongation was not addressed in the clinical pharmacology section. Regarding the QT issue, this reviewer consulted Dr. Mary Parks, Deputy Division Director of DMEDP. According to Dr. Parks, the sponsor did not specifically mention QT prolongation as a safety concern. In addition, Dr. Parks indicated that the safety database was bolstered by the hypertriglyceridemia one that she just reviewed for this NDA. From what she has seen in this NDA and what she has read in the literature, she concluded that she does not have any evidence that Omacor prolongs QT interval.

b(4)

3) Is the dose selected by the sponsor well justified?

The selected dose of 4 g per day was used in most Phase 3 trials. The dose response was evaluated in a Phase 2 study over the dose range of 2 to 8 g per day. It was found that triglyceride tended to decrease as dose increased. However, the reduction in triglyceride levels were not significantly different between placebo, 2 g, 4 g, or 8 g treatment groups.

It was noted that since Omacor was approved for hypertriglyceridemia in Norway in 1995, it has been approved in France, Austria, Germany, Greece, UK, Philippines, Thailand, Spain, Portugal, Ireland, Belgium, Holland, Luxemburg, Switzerland, Cyprus, Czech Republic, and Poland. The approved doses of Omacor for hypertriglyceridemia were 2 to 4 g per day.

However, 2 g dose was not well studied in this submission.

4. PK characteristics of the drug

The pharmacokinetic characteristics of free fatty acid were not being able to be evaluated due to the low level in plasma. Instead, levels of EPA and DHA in serum phospholipids were measured as a marker for absorption.

1) What is the PK of the drug in healthy volunteers?

In healthy subjects (CK85-001), absorption of Omacor® was evidenced by the change of fraction of EPA and DHA in total serum phospholipids as shown in **Table 2**.

Table 2. Mean(SD) percentage EPA and DHA in serum phospholipids

Treatment, daily Dose	EPA (%)		DHA (%)	
	Baseline	Day 15	Baseline	Day 15
K85, 4 g	1.3 ± 0.2	6.2 ± 1.0	5.1 ± 1.0	9.2 ± 0.7
K85, 8 g	1.3 ± 0.6	10.3 ± 1.3	5.5 ± 1.0	10.3 ± 1.1
K85, 14 g	1.2 ± 0.7	11.0 ± 2.7	4.4 ± 0.7	8.5 ± 1.0

Since no electronic dataset was available for this study, preliminary review was conducted. This is an old study conducted in 1987. It was an open-label, sequential group, multiple dose study. The doses of 2, 4, and 7 g Omacor were given to healthy subjects twice daily for 14 days. Plasma samples were collected on day 1 and 14 for the determination of EPA and DHA. Twenty-four subjects were assigned to 3 groups of 8 subjects received doses of either 2, 4, or 7 g of K85 twice daily. The absorption of EPA and DHA was evaluated as percentage in total serum phospholipids. It is concluded that treatment with K85 induced dose-dependent and nonlinear increases in serum EPA content. Intake of 14 g daily provided only marginally higher EPA values than 8 g daily, suggesting that the degree of incorporation of EPA into serum phospholipids was saturated at dose levels greater than 8 g daily. The DHA increase was not dose dependent.

2) What are the mechanism of drug absorption and metabolism?

EPA and DHA are metabolized in the same way as other long-chained fatty acids. When ingested, the bulk of omega-3 fatty acids, like all fatty acids, are used to provide energy and are stored in adipose tissue; small amounts are incorporated into cell membranes. The digestion and absorption of omega-3 fatty acids involve three different steps, namely hydrolysis from the alcohol to which they are bound, absorption, and subsequent uptake and incorporation into membranes of various cell types. The hydrolysis of omega-3 ethyl esters by esterases in the intestine is complete and rapid. After hydrolysis, the free fatty acids (FFAs) are absorbed in the enterocytes where they are rapidly reesterified, and from which they enter the circulation as chylomicrons. Following transit through the thoracic duct, the chylomicrons enter the plasma. The normal half-life of chylomicrons in the circulation is approximately 10 minutes. The enzyme lipoprotein lipase,

which is present on the endothelial surfaces of capillary beds in all tissues, including adipose tissue and skeletal muscle, hydrolyzes the triglyceride core of the chylomicron, liberating the fatty acids for tissue uptake.

2.3 Intrinsic Factors

1. What is the PK in patients with hyperlipidemia?

Nonlinear relationship between dose and EPA or DHA percent increase was demonstrated over the dose range of 2 to 8 g per day in patients with hyperlipidemia.

The dose-concentration relationship was characterized in a Phase 2 study CK85-013. This was a randomized, double-blind, placebo-controlled, parallel-group study in 69 hyperlipidemic patients who were given 2, 4, or 8 g daily for 8 weeks. Absorption of EPA and DHA was evaluated as incorporation of EPA and DHA into serum phospholipids. It was expressed as amount of EPA and DHA in serum phospholipids. Results of percentage change in EPA and DHA are presented in **Table 3** and **Figure 1**.

Study results showed that as the K85 doses increased, the incorporation of EPA was increased, but the increase was less profound when the doses of 4 g and 8 g were compared. Statistical analysis showed that EPA and DHA levels were significant higher for Omacor treated patients than placebo. The increase in DHA incorporation was higher in Omacor treated patients, however, the change was not dose dependent.

Table 3. Dose-concentration relationship in patients with hyperlipidemia

Daily Dose (g)	No. of Subjects	Absolute increase in EPA (mg/L)	Absolute increase in DHA (mg/L)	Increase of EPA (%)	Increase of DHA (%)
0	17	4.84 ± 15.02	3.93 ± 16.42	42 ± 89	7 ± 22
2	14	31.86 ± 12.08	17.65 ± 19.76	181 ± 103	23 ± 24
4	15	60.09 ± 28.21	32.36 ± 25.03	335 ± 249	42 ± 37
8	20	83.97 ± 35.96	25.27 ± 27.52	444 ± 275	38 ± 44

2. What intrinsic factors influence exposure and what is the impact of any differences in exposure on efficacy or safety response?

Based on population based subanalyses, the uptake of EPA in the 4 g K85 treated patients was higher in female than males while the uptake of DHA was similar. The uptake of EPA and DHA was age independent (>=49 years vs. <49 years).

The EPA and DHA levels in serum phospholipids after administration of 4 g K85 daily were examined in several clinical trials, which were randomized, double-blind, placebo (corn oil) controlled clinical trials in patients with hyperlipidemia. Data from these trials are presented in **Table 4**. The following studies were included: CK85013, CK85014, CK85017, CK85019, CK85022, CK85023, K8595014, K8595011, K8595012 (**Table 4**).

Table 4. Pooled Mean (SD) Pharmacokinetics in Patients with hyperlipidemia from 9 clinical trials

Study No.	No. receiving K85	Dose (g)	Treatment duration (weeks)	Increase of EPA (%) Mean ± SD	Increase in DHA (%) Mean ± SD
CK85-013	15	4	8	335 ± 249	42 ± 37
CK85-014	54	4	12	412 ± 282	51 ± 48
CK85-017	29	4	12	363 ± 268	62 ± 37
CK85-019	26	4	12	329 ± 192	35 ± 26
CK85-022	30	4	12	333 ± 203	36 ± 32

CK85-023	28	4	12	210 ± 217	17 ± 31
K85-95014	30	4	24	361 ± 218	54 ± 43
K85-95011	49	4	12	330 ± 264	54 ± 47
K85-95012	12	4	6	158	38

In patients with hyperlipidemia, administration of K85 4 g daily for 8 weeks to 2 year resulted in statistically significant increases in EPA and DHA content in serum phospholipids from baseline compared to placebo. The relative concentrations of EPA and DHA in serum phospholipids were approximately 2 to 5 fold and 1.2 to 1.6 fold, respectively, than those measured at baseline.

Subanalyses of K85 pharmacokinetics based on gender and age were conducted. Results are provided in **Table 5** and **Figures 3 and 4**.

Table 5. Summary of subanalysis of mean (+SD) change and percentage change of EPA and DHA from baseline to the end of the study

		Change in EPA (mg/L)	Change in DHA (mg/L)	Percent change in EPA (%)	Percent change in DHA (%)
Sex	Male (N=199)	53.91 ± 28.01	35.57 ± 33.68	303.35 ± 230.79	44.47 ± 42.57
	Female (N=47)	72.14 ± 35.30	40.43 ± 30.68	423.40 ± 237.10	50.21 ± 39.47
Age	<49 years (N=90)	55.59 ± 29.57	40.21 ± 34.63	324.72 ± 256.62	50.24 ± 46.88
	>=49 years (N=156)	58.43 ± 30.79	34.36 ± 32.14	327.19 ± 224.61	42.87 ± 38.77

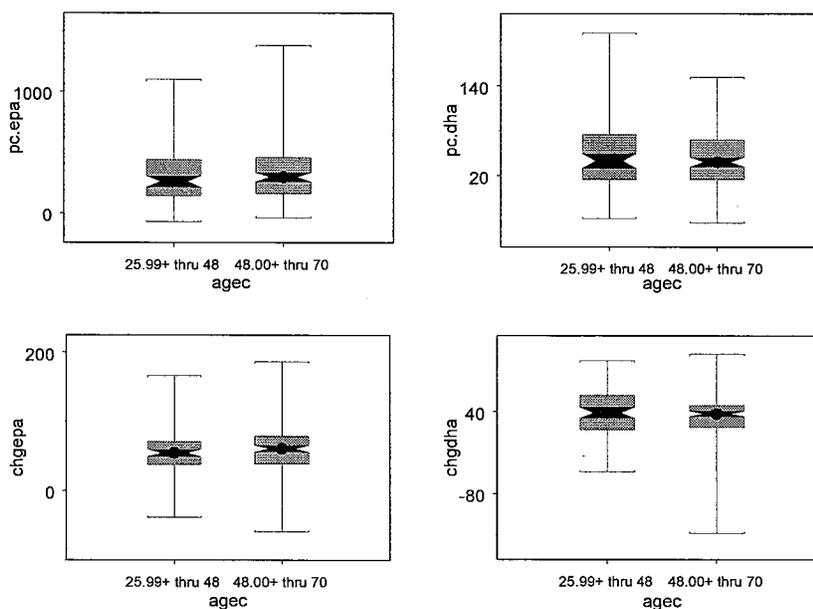


Figure 3. Uptake of EPA and DHA in patients at age groups <49 years and >=49 years. Absolute change in EPA (upper left panel); percent change in EPA (lower left panel); absolute change in DHA (upper right panel); and percent change in DHA (lower right panel)

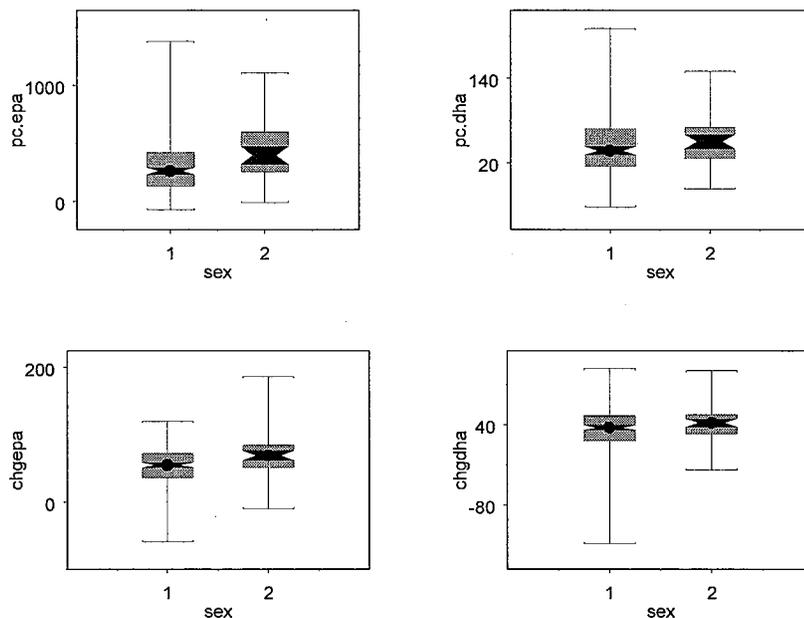


Figure 4. Uptake of EPA and DHA in males and females. Percent change in EPA (upper left panel); absolute change in EPA (lower left panel); percent change in DHA (upper right panel); and absolute change in DHA (lower right panel). Male = 1 and female =2

4. PK in subjects with IgA nephropathy

A published article based on Study K85-95015 showed that percentages of EPA in serum plasma phospholipids were 280% and 480% higher than baseline for 4 g dose and 8 g dose after 6 month treatment, respectively. The percentages of DHA in plasma phospholipids were 76% and 120% higher than baseline for 4 g dose and 8 g dose, respectively.

This study was a randomized, open-label study involving 60 males and 13 females, and who received K85 4 g or 8 g daily for up to 2 years. After 6 months of K85 4 g daily, incorporation of EPA into serum phospholipids (expressed as percentage of EPA in total serum phospholipids) increased 280% over baseline. Incorporation of DHA was 75% over baseline at 6 months. At K85 8 g daily for 6 months, incorporation of EPA into serum phospholipids increased 480% over baseline. Incorporation of DHA was 120% over baseline at 6 months. Since raw data was not included, this study could not be thoroughly reviewed.

Table 6. Estimated means (SD) of EPA and DHA levels at baseline and month 6

		K85-95015	
Time point		4 g Omacor (N=26)	8 g Omacor (N=24)
EPA Levels	Baseline	0.8 (0.5)	0.9 (0.6)
	Month 6	3.1 (1.3)	5.2 (1.8)
DHA levels	Baseline	3.7 (1.5)	3.5 (1.4)
	Month 6	6.5 (1.3)	7.7 (1.6)

Data for each fatty acid are expressed as the weight percentage of total fatty acids and calculated as millimoles per mole divided by 100.

5. PK in subjects with hypertension

A published article based on study CK85-003 showed that after administration of 6 g K85 for 10 weeks, the mean concentrations of EPA and DHA (percentage of EPA or DHA in total serum phospholipids) were increased 154% and 20%, respectively, from baseline.

Study CK85-003 was a 10-week, double-blind, placebo-controlled, parallel-group study in 156 subjects, 94 males and 62 females, with mild/moderate (untreated) essential hypertension and moderate hyperlipidemia. The subjects were randomized to receive K85 or corn oil capsules, each 6 g daily. After 10 weeks of treatment, the EPA and DHA concentrations in serum phospholipids in subjects taking K85 6 g daily had increased significantly from baseline. Since no raw data were included in the submission, this study could not be thoroughly reviewed.

2.4 Extrinsic Factors

1. Is the drug an inhibitor of CYP enzymes?

A mixture of free fatty acid (FFA), EPA/DHA and their FFA-albumin conjugate (23 and 84 μM) inhibited cytochrome P450 activities in human liver microsomes (**Table 7**). However, the inhibition was less than 30% for CYP2A6, 2C9, 2C19, 2D6, 2E1 and 3A at FFA concentrations of 23 μM except 32% inhibition was observed for CYP1A2. It implied that the IC₅₀ values of FFA for all these P450 enzymes would be larger than 23 μM . The sponsor stated that the free forms of the EPA and DHA are undetectable in the circulation following an oral dose of 4 g Omacor. The plasma concentrations of the free form of EPA/DHA, following an infusion of EPA/DHA lipid emulsion to patients was found to be approximately 1 to 5 μM . It is agreed that clinically significant drug-drug interactions due to inhibition of CYPs including CYP1A2, 2A6, 2C9, 2C19, 2E1, or 3A4 are less likely in humans.

In the presence of 23 μM FFA, there was less than 6% inhibition of CYP2A6, 2E1, and 2D6. A 18%, 24%, 32%, and 28% inhibition was seen for CYP3A, 2C19, 1A2, and 2C9, respectively. In the presence of 84 μM of FFA, the activities of CYP3A, 2C19, 1A2, 2C9, and 2A6 were decreased 20%, 43%, 70%, 42%, and 47%, respectively. The inhibition of CYP2D6 and 2E1 activities was less than 10%.

The effect of FFA-albumin on P450 activities was also examined. At the 23 μM concentration, the FFA-albumin conjugate resulted in less than 10% inhibition of CYP3A, 2C19 and 2D6 with a 17% and 68% inhibition being seen for CYP2A6 and 2E1, respectively. Activation was seen with CYP1A2 (26%) and 2C9 (55%). In the presence of 84 μM of FFA-albumin, the activities of CYP2C9, 2A6, 2C19, and 2E1 were decreased 16%, 24%, 46%, and 79%, respectively. The inhibition of CYP3A, 1A2, and 2D6 was less than 12%.

Table 7. Effect of FFA and FFA-Albumin conjugate on Cytochrome P450 Activities in Human Liver Microsomes

CYP Isoform	Assay	% Control Activity			
		FFA		FFA-albumin conjugate	
		23 μM	84 μM	23 μM	84 μM
1A2	Phenacetin o-deethylation	68.1 \pm 3.6	29.9 \pm 7.0	124.9 \pm 4.0	93.2 \pm 9.2
2A6	Coumarin 7-hydroxylation	94.6 \pm 5.4	53.4 \pm 46.4	83.6 \pm 16.8	75.9 \pm 10.7
2C9	Tolbutamide hydroxylation	71.5 \pm 4.8	38.0 \pm 3.8	155.4 \pm 5.3	83.7 \pm 12.0
2C19	S-mephenytoin 4'hydroxylation	76.3 \pm 4.5	57.6 \pm 2.5	96.4 \pm 0.4	54.5 \pm 1.1
2D6	Dextromethorphan o-demethylation	97.5 \pm 2.3	90.4 \pm 0.8	91.3 \pm 3.5	92.5 \pm 3.0
2E1	Chlorzoxazone 6-hydroxylation	108.7 \pm 13.8	107.0 \pm 18.2	32.5 \pm 3.6	20.8 \pm 3.6
3A	Terfenadine hydroxylation/Carboxylation	81.8 \pm 10.7	79.6 \pm 20.2	89.9 \pm 7.7	87.9 \pm 10.0

2.5 General Biopharmaceutics

1. Are ethyl ester and triglyceride forms of Omega-3 fatty acid absorbed differently?

A comparison was conducted in study CK85-002 (Table 8 and 9). The study results showed that both ethyl ester and triglyceride forms were absorbed. Similar increase in EPA and DHA profiles in serum phospholipids were observed when subjects consumed Omacor or TG-30 containing similar amount of EPA and DHA.

Studies CK85-001 and CK85-002 were open-label, multiple dose studies in healthy volunteers conducted in the UK and Norway, respectively. In study CK85-001, 24 healthy male volunteers were divided into 3 groups and given K85 2, 4, 7 g twice daily for 2 weeks. In study CK85-002, 16 healthy volunteers were given a triglyceride preparation TG-30 (Active-EPA) containing 30% omega-3 fatty acids, 12 or 24 g daily for 2 weeks. The increase of EPA and DHA in serum phospholipids is presented in the following table. Data shown are percentages of EPA or DHA in total phospholipids.

Table 8. Comparison of EPA and DHA in K85 and TG30

Product	Daily Dose (g)		
	Oil	EPA	DHA
K85 (ethylester)	4	2.2	1.2
K85 (ethylester)	8	4.4	2.4
K85 (ethylester)	14	7.7	4.2
TG-30 (triglyc.)	12	2.2	1.4
TG-30 (triglyc.)	24	4.4	2.9

Table 9. Uptake of EPA and DHA from K85 and TG-30

Treatment, daily Dose	EPA (%)		DHA (%)	
	Baseline	Day 15	Baseline	Day 15
K85, 4 g	1.3 ± 0.2	6.2 ± 1.0	5.1 ± 1.0	9.2 ± 0.7
K85, 8 g	1.3 ± 0.6	10.3 ± 1.3	5.5 ± 1.0	10.3 ± 1.1
K85, 14 g	1.2 ± 0.7	11.0 ± 2.7	4.4 ± 0.7	8.5 ± 1.0
TG-30, 12 g	1.5 ± 2.1	7.0 ± 1.4	6.5 ± 2.1	8.7 ± 1.8
TG-30, 24 g	1.7 ± 1.4	9.2 ± 0.6	6.8 ± 1.5	9.5 ± 1.2

Both products, K85 and Active-EPA, induced a significant and dose-dependent increase in EPA content. In subjects receiving K85 4, 8, and 14 daily, the increases in mean percentage of EPA in total phospholipids were 4.8, 7.9, and 9.2 times, respectively, over baseline. The increase in incorporation of DHA was not dose-dependent, ranging from 1.8 to 1.9 times over baseline for each group. For Active-EPA 12 and 24 g daily, the increases in mean percentages of EPA were 4.7 and 5.4 fold, respectively, over baseline. Incorporation of DHA for these groups was 1.3 to 1.4 times over baseline.

2. What is the effect of food on the bioavailability of the drug from the dosage form?

No food effect study has been conducted. During clinical studies, the subjects were instructed to take their capsules with a meal.

3. Was the dissolution method and specification adequately justified?

The current proposed method, [redacted] adequately justified:

[redacted] is not

b(4)

Regarding the dissolution method, this reviewer discussed with Dr. Henry Malinowski, DPEII Division Director. Since the drug substance is oil which is insoluble in water, it is concluded that disintegration test is adequate for quality control purpose. The disintegration data were submitted in CMC section and the Chemist reviewer, Dr. Martin Haber found the data acceptable.

2.6 Analytical Section

1. What bioanalytical methods are used to assess concentrations?

The sponsor indicated in their Clinical Pharmacology summary that four different methods for analysis of fatty acid composition were used. These methods were used by the 4 laboratories in which they were performed: [redacted]

[redacted] all used similar chromatography (GC) methodologies while [redacted] used a high-pressure liquid chromatography (HPLC) analysis. Studies CK85-013, CK85-014, CK85-017, CK85-019, CK85-022, CK85-023, K8595011, K8595012, and K8595014 had their fatty acid data analyzed at the [redacted]. Studies K8594010 and K8594110 had their fatty acid data analyzed [redacted] and study K8595009 had their data analyzed at [redacted]. There was no record for all the clinical pharmacology studies.

b(4)

The method validation report was provided for Method [redacted] (quantitative determination of EPA and DHA by GC), which was used for quantitative determination of EPA-EE and DHA-EE in omega-3 concentrate.

b(4)

The method validation for analysis of fatty acid composition used in the clinical studies was submitted on September 21, 2004 as an amendment. Considering the measurements of EPA and DHA in serum phospholipids (typically expressed in relative terms) have mainly been used as a marker of absorption and compliance, this GC method is acceptable.

3 Detailed Labeling Recommendations

Under CLINICAL PHARMACOLOGY Section

Mechanism of Action

The mechanism of action of Omacor[®] is not completely understood. Potential mechanisms of action include inhibition of acyl CoA:1,2-diacylglycerol acyltransferase and increased peroxisomal β -oxidation in the liver. Omacor[®] may reduce the synthesis of triglycerides (TGs) in the liver because EPA and DHA are poor substrates for the enzymes responsible for TG synthesis, and EPA and DHA inhibit esterification of other fatty acids.

Pharmacokinetic and Bioavailability Studies

In healthy volunteers and in patients with hypertriglyceridemia (HTG) EPA and DHA were absorbed when administered as ethyl esters. Omega-3-acids administered as ethyl esters (Omacor®) induced significant, dose-dependent increases in serum phospholipid EPA content. Increases in DHA incorporation were less marked and not dose dependent when administered as ethyl esters. Uptake of EPA and DHA into serum phospholipids in subjects treated with Omacor® was independent of age (<49 years vs. ≥ 49 years). Females tended to have more uptake of EPA into serum phospholipids than males. Pharmacokinetic data on Omacor® in children are not available.

Drug Interactions

Cytochrome P450-Dependent Monooxygenase Activities

The effect of a mixture of free fatty acids (FFA), EPA/DHA and their FFA-albumin conjugate on cytochrome P450-dependent monooxygenase activities was assessed in human liver microsomes. At the 23 µM concentration, FFA resulted in a less than 32% inhibition of CYP1A2, 2A6, 2C9, 2C19, 2D6, 2E1, and 3A. At the 23 µM concentration, the FFA-albumin conjugate resulted in a less than 20% inhibition of CYP2A6, 2C19, 2D6, and 3A, with a 68% inhibition being seen for CYP2E1. Since the free forms of the EPA and DHA are undetectable in the circulation (<1 µM), clinically significant drug-drug interactions due to inhibition of P450 mediated metabolism by EPA/DHA combinations are ——— in humans.

b(4)

Under PRECAUTIONS Section Drug Interactions subsection

Cytochrome P450-Dependent Monooxygenase Activities Omega-3 fatty acid containing product has shown to increase hepatic concentrations of cytochrome P450 and activities of certain P450 enzymes in rats. The induction potential of Omacor on P450 activities in humans is

b(4)

4 Appendix

4.1 Cover Sheet and OCPB Filing/Review Form

Office of Clinical Pharmacology and Biopharmaceutics New Drug Application Filing and Review Form			
General Information About the Submission			
	Information		Information
NDA Number	21-654	Brand Name	Omacor®
OCPB Division (I, II, III)	II	Generic Name	Omega-3-acid ethyl esters
Medical Division	510	Drug Class	Lipid lowering
OCPB Reviewer	Wei Qiu, Ph.D.	Indication(s)	As an adjunct to diet to reduce triglyceride levels
OCPB Team Leader	Hae-Young Ahn	Dosage Form	capsules
Related IND(s)		Dosing Regimen	1 g
Date of Submission	Jan 9, 2004	Route of Administration	Oral
Estimated Due Date of OCPB Review	Sept 24, 2004	Sponsor	Ross Products Division, Abbott Laboratories
PDUFA Due Date	Nov. 12, 2004	Priority Classification	standard
Division Due Date	Oct. 1, 2004		
Clin. Pharm. and Biopharm. Information			

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:	x	2		One in healthy subject and one is patients with hyperlipidemia
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
Mutual:				
In-vitro:	x			Not included.
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				
hyperlipidemia	x	10		Baseline and endpoint serum concentrations only
hypertension	x			literature
IgA nephropathy	x			literature
Meta Analysis:				
PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:	x			Literature
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics				
Absolute bioavailability:				
Relative bioavailability -				
solution as reference:				
alternate formulation as reference:	x	3		
Bioequivalence studies -				
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				

Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		15		
Filability and QBR comments				
	"X" if yes	Comments		
Application filable ?	x			
Comments sent to firm ?		<ol style="list-style-type: none"> 1. The sponsor should submit all the validation for GC and HPLC methods for analysis of EPA and DHA. 2. The sponsor should submit datasets for studies CK85-001, CK85-002, CK85-007, and K85-91003/K85-92006. 3. The sponsor should submit dataset used for population pharmacokinetics and pharmacodynamics analysis. 4. The sponsor should submit complete study report for population pharmacokinetics and pharmacodynamics and study report for pooled analysis of dose proportionality. 5. The sponsor should submit in vitro drug-drug interaction data and report. 		
QBR questions (key issues to be considered)		<ol style="list-style-type: none"> 1. Relative bioavailability 2. Dose proportionality 3. Bioavailability in patients with hyperlipidemia, hypertension and IgA nephropathy 4. Population PK and PD analysis 		
Other comments or information not included above				
Primary reviewer Signature and Date				
Secondary reviewer Signature and Date				

On Jan 9, 2004, Ross Products Division, Abbott Laboratories Inc. submitted an original NDA Omacor® (Omega-3-acid ethyl esters) capsule 1 g as an adjunct to diet to reduce triglyceride levels. Each capsule contains one gram of omega-3-acid ethyl ester drug substance consisting of at least 900 mg of omega-3-ethyl esters. These are predominately comprised of approximately 840 mg of the ethyl esters of eicosapentaenoic acid (EPA), approximately 465 mg and docosahexaenoic acid (DHA), approximately 375 mg.

There were 4 PK studies conducted in support of this application. In 11 efficacy trials, serum lipid concentrations were determined at baseline and endpoints.

1. CK85-001: Ethylester K85: a 14 day multiple dose rising tolerance study
2. CK85-002: Absorption of different forms of omega-3 fatty acids in man-comparison between an ethylester (K85) and a triglyceride (TG30)
3. CK85-007: Comparative effects of prolonged intake of highly purified fish oil as ethyl-ester or triglyceride on lipids, hemostasis, and platelet function in normalipemic men

4. K85-91003/K85-92006: Bioavailability of omega-3 fatty acids, a double blind comparison of three different concentrates

Results of these studies are summarized as followings:

1. CK85-001: After 2 week treatment, in subjects receiving K85 4, 8, and 14 g daily, the increases in mean percentages of EPA in total serum phospholipids were 4.8, 7.9, and 9.2 times, respectively, over baseline. The increases in incorporation of DHA were less marked and not dose dependent, ranging from 1.8 to 1.9 times over baseline for each group.
2. CK85-002: For active-EPA 12 and 24 g daily, the increases in mean percentages of EPA in total serum phospholipids were 4.7 and 5.4 times, respectively, over baseline. Incorporation of DHA for these groups was 1.3 to 1.4 times over baseline.
3. CK85-007: In subjects receiving 4 g of K85 or an equivalent amount of EPA/DHA as a triglyceride compound (Active-EPA) for 7 weeks, there was similar increases in percentages of EPA (~3 times) and DHA (~1.5 times) in serum phospholipids. The investigators concluded that omega-3 fatty acids were equally well absorbed as either ethyl esters or triglycerides.
4. K85-91003/K85-92006: Subjects received 5.1 g of omega-3 fatty acids per day for 2 weeks. The first group received a 62.5% ethyl ester concentrate, the second group received an 80% ethyl ester concentrate, and the third group received an 84% ethyl ester concentrate (K85). There was a clear tendency towards a higher increase in the group receiving the most concentrated formulations of omega-3 fatty acids (mean relative increases from baseline: 62.5% ethyl ester group=308%; 80% ethyl ester group =345%; and 84% ethyl ester [K85] group=417%). The mean absolute increase in serum phospholipid EPA content in the group receiving K85 was higher than the increases observed in the groups receiving 62.5% and 80% ethyl ester groups.

The sponsor indicated that they conducted a pooled analysis for dose proportionality over the range of 2, 4, 6 and 8 g per day using data from studies CK85-012, CK85-013, K85-92004, CK85-014, CK85-017, CK85-019, CK85-022, CK85-023, K85-95014, K85-95011, K85-95012. In the pooled analysis, changes from baseline in EPA uptake were dose proportional for K85 2, 4, and 8 g daily. The change from baseline for K85 6 g daily was equivalent to that at 4 g daily. For DHA, the change from baseline in uptake was highest at K85 4 g daily. Subjects receiving K85 8 g daily showed similar DHA levels to those receiving K85 4 g daily.

In the following efficacy trails, serum concentrations of EPA and DHA were determined at baseline and endpoint to evaluate treatment compliance: CK85-013, CK85-014, CK85-017, CK85-019, CK85-022, CK85-023, K85-92004, K85-94010, and K85-94009. According to the sponsor, a population pharmacokinetics and pharmacodynamics analysis was conducted. It was concluded that treatment effects on mean percent change from baseline to the end of the study in EPA/DHA incorporation in the K85 treated subjects were independent ($p < 0.001$) of gender, age (≥ 49 years vs. < 49 years), diabetic status, and hypertensive status. The percent change from baseline in EPA uptake was less pronounced in the US and Norway subject populations compared to subjects from Sweden, England, and Holland. For DHA, the percent increase in uptake in US subjects was 2 to 4 times larger than for subjects from any European country examined.

The following literatures were included in this NDA:

1. CK85-006: Absorption of the n-3 eicosapentaenoic and docosahexaenoic acids as ethyl esters and triglycerides by humans
This is an open-label, placebo-controlled, crossover design with a 1- to 2-week washout period between each dose. It was performed in 5 healthy volunteers, 2 females and 3 males. All participants received 4 different "fatty meals" in a fasting state in the morning consisting of different fatty acid preparations: (1) 40 g EPAX-5000TG (triglyceride ester of omega-3 fatty acid); (2) 28 g K85; (3) 28 g K85 + 12 g olive oil; (4) 40 g olive oil (placebo meal). The investigated concluded that both formulations of omega-3 (ethyl ester and triglyceride) were

equally well absorbed into different lipid classes in serum. Concomitant ingestion of other unsaturated fatty acid compounds (eg., olive oil) did not affect the absorption of omega-3 fatty acids from K85.

2. CK85-027: Bioavailability of Omega-3 fatty acids: ethylester preparations are as suitable as triglyceride preparations
In subjects receiving equivalent total amount of omega-3 fatty acids, triglycerides containing 32% omega-3 fatty acids (6 g daily), ethyl esters containing 54% omega-3 fatty acids (3 g daily), or ethyl esters containing 84% (K85) omega-3 fatty acids (2 g daily). After 7 to 14 days, EPA levels has risen 5 to 6 times over baseline in all 3 treatment groups. Increases of 2 times over baseline in DHA levels were observed for the triglyceride and the 84% ethyl ester groups, and an increase of 1.7 times over baseline in DHA levels was observed for the 54% ethyl ester group.
3. CK85-003: Effect of eicosapentaenoic and docosahexaenoic acids on blood pressure in hypertension
Administration of K85 2, 4, or 8 g daily for 8 weeks resulted in significantly increased incorporation of EPA and DHA in serum phospholipids compared to placebo. Incorporation of EPA into serum phospholipids was higher in the 8 g group than in the 2 g group, but the extent of incorporation of EPA was similar between the 8 g and 4 g groups. The DHA increases were less marked and not dose dependent. This article concluded that dietary enrichment with 6 g per day of 85% eicosapentaenoic and docosahexaenoic acids can lower blood pressure in subjects with hypertension.
4. K85-95015: A randomized trial of high-dose compared with low-dose omega-3 fatty acids in severe IgA nephrophthy
After 6 months of K85 4 g daily treatment, incorporation of EPA into serum phospholipids increased 3.9 times over baseline. Incorporation of DHA was 1.7 times over baseline at 6 months. At K85 8 g daily for 6 months, incorporation of EPA into serum phospholipids increased 5.5 times over baseline. Incorporation of DHA was 2.2 times over baseline at 6 months.
5. K85-99023: Early modifications of fatty acid composition in plasma phospholipids, platelets and mononucleates of healthy volunteers after low doses of n-3 polyunsaturated fatty acids

**Appears This Way
On Original**

**This is a representation of an electronic record that was signed electronically and
this page is the manifestation of the electronic signature.**

/s/

Wei Qiu
10/20/04 02:52:59 PM
BIOPHARMACEUTICS

Hae-Young Ahn
10/20/04 03:00:15 PM
BIOPHARMACEUTICS