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APPROVAL PACKAGE FOR:

APPLICATION NUMBER

21-654

Medical *REVIEWS*

CLINICAL REVIEW

Application Type NDA 21-654
Submission Number 000
Submission Code 1S

Letter Date January 9, 2004
Stamp Date January 12, 2004
PDUFA Goal Date November 12, 2004

Reviewer Name Mary H. Parks, MD
Review Completion Date October 1, 2004

Established Name omega-3-acid ethyl esters
(Proposed) Trade Name Omacor®
Therapeutic Class lipid-lowering
Applicant Ross Products
Priority Designation Standard

Formulation soft-gel capsules, 1 g
Dosing Regimen 4 g per day
Indication hypertriglyceridemia
Intended Population adults with Type: V

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**APPEARS THIS WAY
ON ORIGINAL**

1 EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

The applicant is proposing an indication for Omacor® (K85) 4 gram per day for the treatment of hypertriglyceridemia in patients. Omacor® is an effective Tg-lowering agent for these three types of dyslipidemia; however, a more favorable effect on the overall lipoprotein profile was observed **only** in the Type V patient population defined by the applicant as those patients having triglyceride (Tg) levels ≥ 750 mg/dL.

Consequently, this application should be “unbundled” into two separate applications with the following separate indications:

1. As an adjunct to diet to reduce TG levels in adult patients

2.

This reviewer recommends approval for the first application in patients with elevated Tg levels in Type V dyslipidemia.

This reviewer recommends a [] action for the second indication. []

1.2 Recommendation on Postmarketing Actions

1.2.1 Risk Management Activity

None. No safety signals were noted in the marketing application which would require specific post-marketing safety evaluation other than outlined under 21 CFR 314.80.

1.2.2 Required Phase 4 Commitments

none

1.2.3 Other Phase 4 Requests

none

1.3 Summary of Clinical Findings

1.3.1 Brief Overview of Clinical Program

This application contained clinical data from the following 5 sources:

Category 1 Studies – these are double-blind, parallel, placebo-controlled studies or parts of studies in patients with hypertriglyceridemia, which used K85 4 g per day. Case report forms were available for these studies. A total of 8 studies comprised this category; these studies were considered pivotal to the efficacy claims of K85.

Category 2 Studies – these are controlled studies or controlled parts of other studies in patients with hypertriglyceridemia which used K85 at doses other than 4 g per day OR used study designs other than placebo-controlled. Case report forms were available for these studies. A total of 11 studies comprised this category.

Category 3 Studies – these are uncontrolled, extension studies or uncontrolled parts of studies in patients with hypertriglyceridemia. Case report forms were available for these studies. A total of 5 studies comprised this category.

Category 4 Studies – these are studies for indications other than treatment of hypertriglyceridemia but where Tg levels are also available. No CRFs were available. A total of 18 studies comprised this category.

Other Studies – this category included published studies for other indications, studies in healthy volunteers, and unpublished studies for other indications. No CRFs were available. A total of 27 studies comprised this category.

The review of efficacy focused primarily on the 8 pivotal studies under Category 1. Four hundred and fifty-four (454) subjects enrolled in these studies with the duration of double-blind treatment ranging from 6 to 16 weeks. The study population in these pivotal studies included patients with a range of Tg levels which enabled further analyses of efficacy based on the different lipid derangements. Dyslipidemic classifications included:

- Type IIb: $177 \text{ mg/dL} < \text{Tg} \leq 750 \text{ mg/dL}$ and $\text{LDL-C} > 160 \text{ mg/dL}$
- Type IV: $177 \text{ mg/dL} < \text{Tg} \leq 750 \text{ mg/dL}$ and $\text{LDL-C} \leq 160 \text{ mg/dL}$
- Type V: $\text{TG} > 750 \text{ mg/dL}$

The review of safety focused primarily on the Category 1 studies for controlled safety data. Data for longer term exposure and at different doses of K85 were available in the integrated safety analysis of the Category 1 to 3 studies.

1.3.2 Efficacy

Across the 8 pivotal studies, the median percent reductions in TG from baseline achieved with Omacor® 4 g per day ranged from 17.3% to 47.7% with an overall reduction of 28% that was significantly greater than the change observed in the placebo group (+2.5% from baseline; $p < 0.0001$). Significant reductions were observed across different dyslipidemic patient populations; however, a greater degree of Tg-lowering was observed in those patients with higher baseline Tg values.

Other lipoprotein parameters were evaluated as secondary efficacy parameters including total-C, HDL-C, LDL-C, VLDL-C, apoB, and nonHDL-C. In the overall per-protocol population analysis, K85 treatment resulted in no significant difference in efficacy on these parameters relative to placebo except for LDL-C. Significant increases in LDL-C were observed in all studies. The clinical relevance of these LDL increases is not known. While the applicant asserts that these changes are secondary to a shift from smaller, more atherogenic LDL particles to larger, less atherogenic ones, such data were not collected in the pivotal studies. Further analyses of LDL/HDL ratios and individual review of patients who had increases in LDL-C suggest that for some individuals, this increase in LDL-C is associated with an increase in atherogenic biomarkers including non-HDL-C and apo B levels.

Subgroup analyses by dyslipidemic classification demonstrated more favorable lipid-altering in the Type V dyslipidemic population whose primary lipid derangement was Tg elevation. These patients achieved significantly greater reductions in Tg, TC, VLDL-C, and non-HDL-C and significantly greater increases in HDL-C levels. Although percent LDL-C increase was higher in this subgroup, the increase was not statistically different from placebo. In contrast, patients with Types IIb and IV dyslipidemia had less of a reduction in Tg and VLDL-C, and achieved no statistical difference in TC, HDL-C, and non-HDL-C relative to placebo. Furthermore, significant increases in LDL-C to HDL-C ratios were noted in the overall patient population and for patients with Type IV dyslipidemia. Marginally significant increases in this ratio were

observed in the Type IIb population. The following table summarizes the median changes in lipid parameters from baseline in patients with Types IIb, IV, and V dyslipidemia.

Table 1. Median Percent Changes From Baseline by Dyslipidemic Type

	TG		TC		HDL		LDL		VLDL		nonHDL	
	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo
Type IIb	-26.3	+2.9	-2.3	-1.5	+5.5	+4.6	+1.4	-3.9	-10.9	+13.7	-3.2	-2.1
Type IV	-25.5	+4.5	+2.0	+1.1	+11.1	+2.9	+33.8	+2.2	-34.3	+6.7	+1.4	+1.0
Type V	-39.4	+2.8	-16.5	+0.5	+18.1	-4.6	+42.8	+19.9	-31.9	+2.2	-18.9	+0.7

In conclusion, K85 4 g daily effectively lowers Tg levels in patients with Types IIb, IV, and V dyslipidemia. However, for Type IIb and IV patients who have elevations in both LDL-C and Tgs, the propensity for K85 to increase LDL-C may offset any benefit achieved with Tg reduction.

Type V dyslipidemic patients treated with K85 for Tg-lowering should have close monitoring of their LDL-C and if increases exceed the their goals based upon NCEP Treatment guidelines, appropriate measures should be taken (e.g., initiation of LDL-lowering drugs or re-evaluate effectiveness of K85).

1.3.3 Safety

Controlled safety data were available in 226 patients treated with K85 4 g/day. A total of 665 patients received K85 therapy (any dose) in studies for which case report forms were available. The average duration of treatment was 19.3 weeks with fewer than 100 patients receiving treatment beyond 48 weeks.

More patients treated with K85 experienced an AE compared to placebo (35.4% vs. 27.6%); however, only 8 patients on drug treatment discontinued as a result of an AE. The incidence of serious AEs was similar between K85 (3.1%) and placebo (2.6%). There were a total of 5 deaths (4 in K85 and 1 in placebo). All were CV-related except one patient on K85 who committed suicide. Review of the individual death narratives did not suggest any relationship between the event and drug treatment.

The most common AEs (by preferred term) in the K85 group were eructation (4.9%) followed by infection (4.4%), flu syndrome (3.5%), and diarrhea (3.5%). For all patients exposed to K85, AEs were reported more commonly for the digestive system (15%).

Adverse events by dyslipidemic type (IIb, IV, and V) were also evaluated. Similar to the overall safety evaluation, rates of AEs occurred more frequently in the K85 treatment group than placebo, with the percentage of subjects who experienced at least one treatment-emergent AE highest in the Type IIb patient population. However, the majority of these cases occurred in the

digestive body system. There were no marked differences in the incidence rates of SAEs across the three dyslipidemic groups.

Safety evaluation by gender and age also showed a similar pattern. AEs were higher in the K85 treatment group compared to placebo for males and females and for patients < 60 years and ≥ 60 years of age. Again, the most common AEs reported were in the digestive body system.

Laboratory evaluations did not identify any clinically relevant changes in the hematologic or serum chemistry studies, including hepatic transaminases.

Although the duration of treatment is shorter than typical lipid-altering marketing applications, omega-3-fatty acids, including DHA and EPA, are available in the U.S. as dietary supplements. Omacor® has been available in numerous foreign countries for different indications as early as 1994. This product has marketing approval for hypertriglyceridemia in 14 countries (Norway, France, Austria, Germany, Greece, UK, Philippines, Thailand, Spain, Portugal, Ireland, Belgium, Holland, and Luxemburg).

No approved marketing application has been withdrawn due to safety or efficacy concerns and no marketing application has been denied due to safety concerns. The applicant reports that no spontaneous reports of AEs or SAEs have been reported to Pronova Biocare and /or its licensees between January 1, 1994 and September 1, 2002.

In conclusion, no serious safety concerns were identified in this application. More patients taking K85 experienced gastrointestinal side-effects, primarily eructation, diarrhea, and nausea; however, none of these AEs was serious nor was there a high rate of drug discontinuation.

1.3.4 Dosing Regimen and Administration

This application proposes that only Omacor® 4 g daily be administered with meals for the treatment of hypertriglyceridemia. The dose can be administered as a single 4-gram dose or two 2-gram doses. A pooled analysis of all pivotal studies and 4 non-pivotal studies allowed for the assessment of efficacy across a K85 dose range of 2, 3, 4, 5, and 8 gram per day. Significant reductions in Tg were achieved with the 3, 4, 6, and 8 gram per day groups but not at the 2 gram daily dose.

Table 2. Efficacy by Dose of K85

	K85 – 2g n=75	K85 – 3 g n=61	K85 – 4 g n=206	K85 – 6 g n=18	K85 – 8g n=6	Placebo
Baseline median Tg, mg/dL	293.2	757.1	422.8	587.1	251.5	412.0
Mean % chg from baseline	-4.2	-20.4	-28.0	-30.5	-44.5	+1.4
Median % chg from	-12.2	-24.9	-31.2	-28.9	-43.2	-3.0

baseline						
p-value	0.9947	0.0007	<0.0001	0.0027	0.0192	---

1.3.5 Drug-Drug Interactions

In vivo metabolic drug-drug interactions via inhibition of major cytochrome P450 isoenzymes are not expected with Omacor®. No data are available to determine if EPA or DHA will induce P450 isoenzymes.

1.3.6 Special Populations

Approval of Omacor® as a prescription drug is limited to only those adult patients with severe hypertriglyceridemia in the Type V category. No pediatric studies have been conducted with this product and Type V dyslipidemia is not observed in the pediatric patient population. Efficacy and safety analyses in patients younger than 60 years of age versus those ≥ 60 years and in males versus females revealed no differences.

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2 INTRODUCTION AND BACKGROUND

2.1 Product Information

Omacor® is an oral capsule formulation of purified fish oil that contains the omega-3-fatty acids, eicosapentanoic acid (EPA) and docosahexaenoic acid (DHA) in approximately 465 mg and 375 mg amounts, respectively. In addition, each capsule contains approximately 4 mg of α -tocopherol.

The manufacturer of the drug substance is Pronova Biocare in Norway. The US Agent for this NDA is Ross Products Division, Abbott Laboratories in Columbus, Ohio.

The applicant is proposing the following indications:

[
]]
[
]]
Omacor® is indicated as an adjunct to diet to reduce TG levels in adult patients

[
]]
The hypotriglyceridemic effect of omega-3-fatty acids is not entirely known but studies suggest that this may be due to a reduction in endogenous Tg-rich lipoprotein production (e.g., decreased VLDL-C), increased Tg removal via lipoprotein lipase (LPL), or a combination of both.

2.2 Currently Available Treatment for Indications

Currently approved therapies for hypertriglyceridemia include the fibric acid derivatives (primarily gemfibrozil and fenofibrate), niacin and nicostatin (niacin/lovastatin), and HMG-CoA reductase inhibitors or statins (pravastatin, simvastatin, atorvastatin, and rosuvastatin). The statins are approved for lowering Tg in patients with Fredrickson IIa/IIb and IV dyslipidemia while the fibric acid derivatives and niacin also have indications to lower Tg in the Type V dyslipidemic population.

The range of Tg lowering is highly variable across these different therapies with greater Tg-lowering observed with the fibrates and niacin over the statins. A greater reduction is also observed for patients with more severe hypertriglyceridemia (e.g., Type V vs. Type IIb).

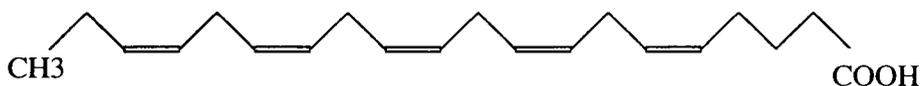
Safety concerns associated with the use of these products include myopathy with rare cases of rhabdomyolysis that may cause acute renal failure or death. This risk may increase with the combined use of a fibrate and statin or when the statin is co-administered with a drug which inhibits its metabolism. Other safety concerns include warfarin interactions with the fibrates and hepatic transaminase elevations with both the statins and fibrates.

2.3 Availability of Proposed Active Ingredient in the United States

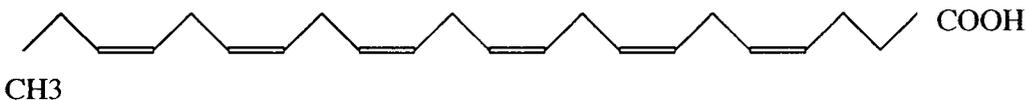
Products containing the omega-3-fatty acids, DHA and EPA, are available as dietary supplements in the United States.

Omega-3- and omega-6-fatty acids are essential polyunsaturated fatty acids. The latter is abundant in Western diets, particularly in vegetable oils rich in linoleic acid. Humans cannot convert omega-6-fatty acids to omega-3-fatty acids hence the latter must be obtained from separate dietary sources. The primary dietary source of omega-3-fatty acids is fish and fish oils. Fish oil contains approximately 30% EPA and DHA in a triacylglycerol form whereas the omega-3-fatty acids contained in Omacor® are as ethyl esters.

The omega-3-fatty acids have their first double bond at the third carbon molecule from the methyl end of the fatty acid. The chemical names of these fatty acids identify the number of carbon atoms, the number of double bonds, and the position of the first double bond. For example, eicosapentanoic acid (EPA) has the chemical name: C₂₀:5n-3. EPA has 20 carbon atoms with 5 double bonds; the first double bond is at the 3rd carbon atom. The chemical structure corresponding to the chemical name is:



Docosahexanoic acid (DHA) is also C₂₂:6n-3 and would therefore have 22 carbon atoms, 6 double bonds, with the first one at the 3rd carbon position. The chemical structure for DHA is:



2.4 Important Issues With Pharmacologically Related Products

Many articles have been published regarding the CV protection associated with omega-3-fatty acids. Epidemiologic and population studies have demonstrated an inverse relationship between consumption of fish and fish oil and the incidence of coronary heart disease. Prospective clinical

studies suggest a reduction in risk of recurrent CV events in patients with established heart disease associated with the administration of low doses of omega-3-fatty acids (1 gram daily). The biochemical basis for the observed cardioprotective effect has not been established but anti-thrombotic, anti-hypertensive, anti-arrhythmic, anti-inflammatory, and hypotriglyceridemic effects have all been proposed as contributing factors.

The anti-thrombotic effect of polyunsaturated fatty acids is thought to be secondary to inhibition of platelet aggregation. Typically, cyclooxygenase in platelets converts arachidonic acid (AA) to the prostaglandin thromboxane A2 (TXA2) which is a platelet aggregator and vasoconstrictor. Conversely, lipoxygenase in endothelial cells converts AA to prostacyclin I2 (PGI2), a vasodilator and inhibitor of platelet activation. Thus, TXA2 and PGI2 interact to maintain balanced hemostatic activity. EPA from fish oil can serve as a substrate for cyclooxygenase and lipoxygenase with the production of thromboxane A3 (TXA3) and prostacyclin I3 (PGI3) instead of TXA2 and PGI2. Neither of these by-products has platelet aggregating properties which may contribute to the anti-thrombotic effects of omega-3-fatty acids.

2.5 Presubmission Regulatory Activity

Omacor® has been reviewed by the Agency under IND 45,998 (for hypertriglyceridemia) L

The applicant has had several meetings with the Division of Metabolic and Endocrine Drug Products regarding a development program for the treatment of hypertriglyceridemia under IND 45,998. Meetings for which minutes are available are summarized below:

Table 3. Summary of Regulatory Meetings

Type of Meeting	Date of Meeting – key issues discussed
Type B Guidance Meeting	October 20, 2003
PreNDA Meeting	October 31, 2001

In both these meetings, the format and content of an NDA submission for hypertriglyceridemia were discussed. The sponsor was asked to submit published literature that would associate omega-3-fatty acid intake with clinical CV benefit; however, the sponsor was made aware that such data would not support a labeling claim beyond that of lipid-altering. Other meetings for which minutes are not available include meetings on July 20, 1993, April 14, 1994, and March 14, 1996.

2.6 Other Relevant Background Information

2.6.1. Proposed Proprietary Name

The Division of Medication Errors and Technical Support raised objections to the tradename, Omacor®, citing concerns with two look-alike/sound-alike drugs: Inocor and Amicar. Inocor is no longer marketed in the United States and will, therefore, not be a potential cause for medication errors with Omacor. Amicar is aminocaproic acid, a hemostatic agent used to improve hemostasis in patients who have defects in primary hemostasis. It is available as in a parenteral formulation for intravenous administration and oral formulation as a syrup and tablets. The oral administration of Amicar would also include a dosage strength that overlaps the proposed dosing for Omacor.

This reviewer noted that the sponsor included results of clinical studies that have demonstrated increases in bleeding time that never exceeded normal limits. No clinically relevant bleeding tendencies associated with Omacor® use were noted in this NDA review. The applicant stated that this product has been available in other countries under the same name. To their knowledge, no safety reports have been received of medication errors between Omacor® and Amicar®. They also noted that the more commonly used formulation of Amicar® is the parenteral formulation.

Given the extensive use of Omacor® in foreign markets under the same tradename and absence of serious postmarketing safety reports, this reviewer has no objection to the proposed proprietary name.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

See Dr. Martin Haber's review for chemistry-related issues.

3.2 Animal Pharmacology/Toxicology

Preclinical studies were conducted under IND 123456789. ¹ These were re-reviewed by Drs. Indra Antonipillai and Karen Davis Bruno for NDA 21-654. Preclinical studies were generally adequate to support the proposed dosing regiment.

Chronic one-year toxicity studies were performed in rats and dogs. The primary target organs of toxicity were liver in rats and adrenals in dogs. The NOAEL in rats in both males and females was 2-fold the human dose of 4 gm per day. The NOAEL in male dogs was 0.4x the human dose of 4 gm per day. In females dogs, the NOAEL was 2-fold the same human dose.

Several studies evaluating mutagenic/genotoxic potential were negative.

The 2-year carcinogenicity study was found to be inadequate because the dose studied was < 50% the maximally tolerated dose (MTD) and the study was not carried out to the optimal 2-year duration. The Executive CAC reviewed this study and deemed that no further preclinical studies were required.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

The applicant submitted clinical data from several sources which are categorized as follows:

Category 1 Studies – these are double-blind, parallel, placebo-controlled studies or parts of studies in patients with hypertriglyceridemia which used K85 4 g per day. Case report forms were available for these studies. A total of 8 studies comprised this category; these studies were considered pivotal to the efficacy claims of K85.

Category 2 Studies – these are controlled studies or controlled parts of other studies in patients with hypertriglyceridemia which used K85 at doses other than 4 g per day OR used study designs other than placebo-controlled. Case report forms were available for these studies. A total of 11 studies comprised this category.

Category 3 Studies – these are uncontrolled, extension studies or uncontrolled parts of studies in patients with hypertriglyceridemia. Case report forms were available for these studies. A total of 5 studies comprised this category.

Category 4 Studies – these are studies for indications other than treatment of hypertriglyceridemia but where Tg levels are also available. No CRFs were available. A total of 18 studies comprised this category.

Other Studies – this category included published studies for other indications, studies in healthy volunteers, and unpublished studies for other indications. No CRFs were available. A total of 27 studies comprised this category.

This review evaluated only data from Categories 1 through 3 as those studies classified as Category 4 or as “Other Studies” had no CRFs available and/or were in patients with medical conditions other than hypertriglyceridemia.

4.2 Tables of Clinical Studies

The following tables summarize the clinical studies under Categories 1, 2, and 3.

Table 4. Category 1 Studies

Study Number	Study Duration (wks)	Number of Subjects Enrolled
CK85-014	12	111
CK85-017	12	55
CK85-019	12	53
CK85-022	12	60
CK85-023	12	57
K85-94010	6	41
K85-95009	16	43
CK85-013	8	34*

*CK85-013 included K85 2g, 4g, and 8g doses. Only the comparison between subjects who received K85 4 g per day and placebo was considered blinded and considered in this category of studies.

Table 5. Category 2 Studies

Study Number	Study Duration (wks)	Number of Subjects	Distinguishing Characteristic from Category 1 Studies
Double-Blind, Parallel, Placebo-controlled Studies using Doses other than K85 4 g per day			
CK85-012	16	41	Used K85 6 g per day
K85-92004	4	135	Used K85 2 g per day
K85-97018	12	49	Used K85 3 g per day
K85-98019	12	48	Used K85 3 g per day
Other Double-Blind Studies of Differing Designs that Used K85 4 g per day			
K85-95011	12	98	Used gemfibrozil active control
K85-95012	6	21	Tg measured as 2 ⁰ endpt
K85-95013	16	15	Crossover design
K85-95014	24	59	Used simvastatin as concurrent therapy
Open-label, parallel studies that used K85			
CK85-013	8	52	Used K85 2g and 8g per day
K85-95109	5 mos	36	Compared K85 2g and 4g per day
K85-95210	6 mos	29	Compared K85 2g and 4g per day

Table 6. Category 3 Studies

Study Number	Study Duration	Number of Subjects	Classification/Characteristics
CK85-112	1 yr	35	open-label extension study to

CK85-113	1 yr	32	CK85-012, a double-blind study: used K85 4 g per day open-label extension study to CK85-013, enrollment delayed by 1-11 mos after conclusion of original study; used K85 4 g per day
K85-92004	4 wks	133	open-label extension following a double-blind study; used K85 3 g per day
K85-94110	1 yr	38	open-label extension to K85-94010 (a category 1 study); used K85 4 g per day
K85-95014	6 mos	46	open-label extension following a double blind study; used simvastatin with K85 4 g per day

4.3 Review Strategy

The efficacy review for Omacor® 4 gram gel capsules for the treatment of hypertriglyceridemia focused on the individual and integrated review of the 8 Category 1 studies. Category 1 studies formed the basis of the efficacy findings in this application. The results from these studies are included in the proposed labeling.

The safety review for this application focused on all the clinical studies for which CRFs were available (Category 1, 2, and 3 studies). Placebo-controlled studies (Category 1 studies) were considered primary sources for safety evaluation; however, studies from other categories were evaluated to assess tolerability and safety beyond 12 to 16 weeks of treatment with K85 and at doses other than 4 g per day.

4.4 Data Quality and Integrity

There was no evidence found for this reviewer to question the quality or integrity of the data submitted. Prior to submission of the NDA, the applicant discussed with the Agency that establishing efficacy would rely on lipid-altering studies conducted earlier by different investigators under Pronova in Norway. While these studies would be pivotal, a large amount of

data would be derived from published literature. Given that the efficacy measures were based on objective laboratory data which could be verified across studies and the literature, no clinical audit was requested.

4.5 Compliance with Good Clinical Practices

There was no evidence found for this reviewer to question the compliance or adherence to good clinical practices in the conduct of these studies. All pivotal clinical studies were conducted under the oversight of an Institutional Review Board and informed consents were required on all study subjects.

4.6 Financial Disclosures

The applicant submitted FDA Form 3454 stating no significant financial arrangements or interests as defined under 21CFR54.1 between investigators of Category 1 studies. As these were the pivotal efficacy studies and the only studies contributing to the placebo-controlled safety database, this reviewer concludes that sufficient documentation has been provided.

5 CLINICAL PHARMACOLOGY

5.1 Pharmacokinetics

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.

5.2 Pharmacodynamics

Drug effectiveness was evaluated in several lipid-altering trials. Results of these trials are summarized under Section 6 of this document.

5.3 Exposure-Response Relationships

Dose-response relationship was demonstrated over a daily dose range of 2 to 8 g with a trend towards greater Tg-lowering with increasing doses. However, insufficient patient exposures across this dose range preclude an adequate review of safety and efficacy for doses other than 4 g per day.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication - Treatment of Hypertriglyceridemia

6.1.1 Methods – Review of Category 1 Studies

This NDA was submitted primarily as a paper submission. This reviewer reviewed the clinical study reports and other relevant information of each of the eight Category 1 studies. These studies were randomized, placebo-controlled studies in which K85 4 g per day was administered to patients with hypertriglyceridemia. Data reviewed are located in the following NDA volumes:

Table 7.

Clinical Study Number	Location of Reports by NDA Volume#
CK85-014	77-82
CK85-017	83-86
CK85-019	87-91
CK85-022	92-95
CK85-023	96-98
K85-94010	99-101
K85-95009	102-104
CK85-013	105-108

The integrated review of efficacy is based on data/information located in NDA volume #151.

The following subject populations were defined for efficacy and safety analyses:

All-subjects population - consisted of all subjects who received study medication.

Intent-to-treat (ITT) population - consisted of all subjects who received at least 1 dose of study medication and had at least 1 subsequent assessment (efficacy or safety)

Per-protocol (PP) population - consisted of all subjects who complied with the study protocol. For the primary efficacy analysis, the PP population included all subjects who received study drug and had the protocol-specified average TG assessments at baseline and at end of study.

Secondary efficacy variables included TC, HDL-C, LDL-C, VLDL-C, ApoA1, and Apo-B; however, not all the protocols had data available for each of these variables. LDL-C levels were not measured but calculated as follows:

- If $Tg < 500$ mg/dL, then $LDL-C = TC - HDL-C - TG/5$
- If $Tg \geq 500$ mg/dL, then $LDL-C = TC - HDL-C - VLDL-C$

For the individual studies, all primary efficacy analyses were performed using nonparametric methods with the PP population. All secondary efficacy analyses were performed using

nonparametric methods with the ITT population and parametric methods with both the ITT and PP subject populations.

For the integrated review of efficacy, the primary and secondary efficacy data were analyzed using a parametric approach (ANOVA) to compare mean values and a nonparametric approach (Wilcoxon two-sample test) to compare median values.

6.1.2 General Discussion of Endpoints

The primary endpoint measure in all the pivotal studies is the change from baseline to end of study in Tg level. Triglycerides are lipids that contain 3 long-chain fatty acid molecules attached to a glycerol backbone. Similar to cholesterol, it is transported in the body by various lipoproteins, including chylomicrons and their remnant particles, IDL-C, and VLDL-C. Hypertriglyceridemia results from abnormalities in the synthesis and/or degradation processes involving these TG-rich lipoproteins.

Elevated Tg levels have been identified as an independent risk factor for CHD. While no clinical outcomes studies have shown that independent lowering of these Tg-rich particles favorably alter the risk of CV mortality and morbidity, the Veterans Affairs High-density Lipoprotein Cholesterol Intervention Trial (VA-HIT) demonstrated a 22 to 23 % relative RR for CHD death and nonfatal MIs associated with the use of gemfibrozil.¹ In this study, clinical benefit was associated with mean reductions in Tg levels of 31% and mean increases in HDL of 6%. Furthermore, approximately one-third of patients with CAD have a lipid profile that includes normal or average LDL-C but elevated Tg and decreased HDL levels. Recognizing the direct role of Tg-rich lipoproteins on CVD, many researchers and scientific organizations have recommended that patients CV risk assessments include a determination of Tg level. In some instances, Tg levels should be a target of therapy - be it diet/lifestyle or pharmacologic interventions. The National Cholesterol Education Program Adult Treatment Panel III (NCEP-ATP III) identified normal Tg levels as being < 150 mg/dL with specific therapy to be considered in those individuals whose Tg levels \geq 200 mg/dL.²

Elevated Tg levels is also associated with an increased risk of pancreatitis. In this situation, Tg levels are typically greater than 1,000 mg/dL.

Tg levels, as an efficacy endpoint, have been evaluated in drug development programs for other lipid-altering drugs including fibric acid derivatives (gemfibrozil, fenofibrate) and HMG-coA reductase inhibitors (or statins). Labeled indications include Fredrickson Type IIb and IV, which is associated with an increase risk for CVD, and Fredrickson Type V, which is associated with an increased risk for pancreatitis. Studies supporting the approval of treating hypertriglyceridemia

¹ Rubins HB et al. Gemfibrozil for the secondary prevention of coronary heart disease in men with low levels of high density lipoprotein cholesterol. *N Engl J Med.* 1999;341:410-418.

² Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). *JAMA.* 2001;285:2486-2497.

in these different patient population have focused on establishing a significant and consistent reduction in Tg levels from baseline relative to placebo without an unfavorable alteration in other lipoprotein parameters. Given the high variability in this lipid measure, efficacy analyses have required averages of several different measures obtained on separate study visits. Tg values in a study population rarely follows a normal distribution, and statistical analyses have compared mean and median values between treatment groups using a nonparametric approach.

6.1.3 Study Design

The 8 double-blind, parallel, placebo-controlled studies evaluated in this integrated review of efficacy are summarized in the following table.

Table 8. Summary of Category 1 Studies

Study Number	Lipid Inclusion Criteria	Treatment Duration	No. of Patients Enrolled on K85	No. of Patients Enrolled on Placebo
CK85-014	TG b/w 177 and 885 mg/dL, inclusive and TC \geq 201 mg/dL	12 wks	54	57
CK85-017	TG b/w 177 and 885 mg/dL, inclusive and TC \geq 201 mg/dL	12 wks	29	26
CK85-019	TG b/w 177 and 885 mg/dL, inclusive and TC < 386 mg/dL	12 wks	26	27
CK85-022	TG b/w 177 and 885 mg/dL and TC \geq 232 mg/dL	12 wks	30	30
CK85-023	TG b/w 177 and 1326 mg/dL, inclusive, and TC \geq 232 mg/dL	12 wks	28	29
K85-94010	TG b/w 500 and 2000 mg/dL	6 wks	20	21
K85-95009	TG b/w 500 and 2000 mg/dL	16 wks	22	21

Study Number	Lipid Inclusion Criteria	Treatment Duration	No. of Patients Enrolled on K85	No. of Patients Enrolled on Placebo
CK85-013	TG b/w 177 and 442 mg/dL and TC \geq 250 mg/dL	8 wks	17	17

All 8 studies had a dietary run-in period that ranged from 4 to 10 weeks, and the duration of the double-blind treatment period ranged from 6 to 16 weeks. The primary efficacy endpoint was change from baseline to end of study in serum TG levels. The baseline value was defined as the mean of at least two measurements obtained on separate visits during the screening period. The end-of-study value was defined as the mean of at least two measurements on separate visits.

6.1.4 Efficacy Findings

6.1.4.1 Demographics and Baseline Characteristics

The demographic characteristics were comparable between the K85 4 g and placebo treatment groups in the Category 1 studies. The majority of study subjects was Caucasian (94-96%) and male (73-74%).

Table 9. Demographic Characteristics in Combined PP Population from Category 1 Studies

Characteristic	K85 n=206	Placebo n=204	p-value
Age, yrs			
mean	52	52	0.9163
median	54	52	
SD	10.29	10.3	
range	26-70	26-70	
Gender, n (%)			
male	153 (74.3)	149 (73.0)	0.7724
female	53 (25.7)	55 (27.0)	
Race, n (%)			
Caucasian	198 (96.1)	192 (94.1)	0.4292
Other	8 (3.9)	11 (5.4)	
Missing	0	1 (0.5)	

Data obtained from Sponsor's Table 16, Section 4.3.2, ISE, NDA volume # 151

The mean and median baseline Tg level for the combined PP population were approximately 413 mg/dL and 307 mg/dL, respectively. Baseline LDL and HDL for the PP population were approximately 170 mg/dL and 34 mg/dL, respectively. Overall, this cohort of patients had moderately elevated LDL-C, elevated Tg, and decreased HDL-C. As the lipid inclusion criteria varied by study, the average baseline TG level varied across the 8 studies with baseline Tg levels being much higher in studies which specifically recruited subjects with Type IV/V hypertriglyceridemia. The following table summarizes the baseline TG levels by treatment groups in the 8 studies.

Table 10. Baseline Lipid Values for the ITT Population by Study

	K85	Placebo
CK85-014 mean TG median TG SD range	294.5 264.5 104.89 ┌	305 258 110.49 ┐
CK85-017 mean TG median TG SD range	305.8 276 106.47 ┌	358.5 340 108.15 ┐
CK85-019 mean TG median TG SD range	295.6 267.5 113.39 ┌	251 238 76.75 ┐
CK85-022 mean TG median TG SD range	343.5 279 149.32 ┌	374.1 305 306.53 ┐
CK85-023 mean TG median TG SD range	358.3 294.5 196.64 ┌	278.2 274.5 104.04 ┐
K85-94010 mean TG median TG	840.1 ┌	823 ┐

	K85	Placebo
SD range	297.66 ┌	286.9 ┐
K85-95009 mean TG median TG SD range	919 817.5 380.79 ┌	872.2 841 265.56 ┐ 1685
CK85-013 mean TG median TG SD range	308.2 299 68.69 ┌	270.2 260 68.94 ┐

Two studies specifically recruited patients with severe hypertriglyceridemia. Patients in K85-94010 and K85-95009 have baseline lipid profiles that are more reflective of the Type IV/V or V patients.

6.1.4.2 Primary Efficacy Results

6.1.4.2.1 By Individual Studies

The effect of K85 treatment on Tg levels is summarized in the following table by study.

Table 11. Tg Lowering Efficacy in Category 1 Studies

	n	median baseline Tg	mean % change from baseline	median % change from baseline	p-value*
CK85-014 K85 4 g placebo	49 46	258 255	-21.9 +3	-25.4 +0.5	<0.0001
CK85-017 K85 4 g placebo	24 23	278 330	-30.6 +11.8	-32.4 +10.5	<0.0001
CK85-019 K85 4 g placebo	26 26	267.5 238	-18.8 +2.2	-17.3 -4.4	0.0033
CK85-022 K85 4 g	28	286	-28.1	-28.7	0.0013

	n	median baseline Tg	mean % change from baseline	median % change from baseline	p-value*
placebo	30	305	+2.5	-6.5	
CK85-023 K85 4 g	28	294.5	-31.8	-31.3	<0.0001
placebo	28	274.5	-2.0	-7.3	
K85-94010 K85 4 g	19	801	-31.4	-38.8	0.0004
placebo	19	725	-3.1	-7.6	
K85-95009 K85 4 g	20	817.5	-43.1	-47.7	<0.0001
placebo	19	863	+15.6	+12.4	
CK85-013 K85 4 g	12	280	-28.1	-30	ND
placebo	13	260	-16.4	-8.2	

*using a nonparametric approach (Wilcoxon two-sample test) comparing median values between treatment groups

The median reductions in Tg levels were significantly greater in the K85 4 g per day group compared to placebo for all the Category 1 studies except CK85-013. This study included 2 other K85 doses: 2 g and 8 g per day. No significant differences were noted between all 4 treatment groups in this trial (2, 4, 8 g and placebo), hence no pairwise comparisons were performed between K85 4 g and placebo in this study.

The range of median % reduction in Tg level from baseline was -17.3% to -47.7%. For each Category 1 study, the K85 4 g per day had reduced mean Tg levels by 4 weeks of treatment and this reduction was maintained for the duration of treatment (Figure 1, section 4.4.5 in Volume 151). There was a trend for greater Tg-lowering in patient populations with higher baseline Tg levels.

6.1.4.2.2 Integrated Primary Efficacy Results

A pooled analyses of all 8 pivotal studies demonstrated an overall significant reduction in Tg levels, both absolute and % change, from baseline for K85 4 g per day relative to placebo. The following table summarizes this pooled analysis for the overall PP population.

Table 12. Mean Change from Baseline in Tg Levels in Combined PP Population

	K85 4 g n=205	Placebo n=204	p-value

Mean Baseline Tg, mg/dL	422.8	404.0	
Mean Endpoint Tg, mg/dL	285.7	410.3	
Absolute chg, mg/dL	-137	+6.3	<0.0001
% chg	-28.0	+2.5	<0.0001

6.1.4.2.3 Tg Lowering by Dyslipidemia Classification and Baseline Tg Levels

A subgroup analysis was performed by dyslipidemia classification as follows:

Type IIb: 177 mg/dL < Tg ≤ 750 mg/dL and LDL-C > 160 mg/dL

Type IV: 177 mg/dL < Tg ≤ 750 mg/dL and LDL-C ≤ 160 mg/dL

Type V: TG >750 mg/dL

Table 13. Mean Change from Baseline in Tg by Dyslipidemia Classification

	K85 4 g	Placebo	p-value
Type IIb Dyslipidemia			
	n=111	n=118	
Mean baseline Tg, mg/dL	294.9	294.4	<0.0001
Mean endpoint Tg, mg/dl	211.8	297.3	
Mean % chg	-26.3	+0.8	
Type IV/V Dyslipidemia			
	n=90	n=77	
Mean baseline Tg, mg/dL	573.6	572.9	<0.0001
Mean endpoint Tg, mg/dl	375.6	583.6	
Mean % chg	-29.4	+4.0	
Type IV Dyslipidemia			
	n=65	n=54	
Mean baseline Tg, mg/dL	381.3	380.8	<0.0001
Mean endpoint Tg, mg/dl	274.3	391.0	
Mean % chg	-25.5	+4.5	
Type V Dyslipidemia			
	n=25	n=23	
Mean baseline Tg, mg/dL	1072.4	1024.1	<0.0001
Mean endpoint Tg, mg/dl	638.8	1035.9	
Mean % chg	-39.4	+2.8	

K85 4 g per day significantly lowered Tg over placebo across the different dyslipidemic patient populations. The effect was greater for those patients with more severe hypertriglyceridemia. An analysis performed by the sponsor using the following cut-offs for baseline Tg level demonstrated a similar response.

Table 14. Efficacy by Range of Tg Elevation

Baseline Tg Level	K85 4 g per day	Placebo
≤ 250 mg/dL	n=63 -19.8%	n=67 +4.9%
251-499 mg/dL	n=90 -27.0%	n=88 +0.9%
500-749 mg/dL	n=28 -39.5%	n=26 +1.5%
≥ 750 mg/dL	n=25 -39.4%	n=23 +2.8%

*p<0.0001 (ANOVA) compared to placebo

6.1.4.2.4 Efficacy Analyses by Gender

The effect of K85 4 g per day on Tgs was significantly greater than placebo for both men and women.

Table 15. Effects of K85 4 g per day by Gender*

	Males		Females	
	K85 4 g n=153	Placebo n=149	K85 4 g n=53	Placebo n=53
Mean baseline Tg	422.5	386.8	423.4	450.7
Endpt Tg	290.8	394.6	270.7	453.0
Mean % chg	-26.6	+1.8	-32.2	+4.4

* Mean % chg from baseline compared to placebo was significant at p<0.0001 (ANOVA) for both males and females

6.1.4.2.5 Efficacy Analyses by Age

Tg lowering effect was analyzed within the subgroups < 60 years and ≥ 60 years. The effect of K85 4 g per day on Tg-lowering was significantly greater than placebo in both age categories with the mean reduction being -29.5% for the <60 yrs age group and -23.6% for the ≥ 60 yrs age group. Placebo groups had +4.0% and -1.6% change from baseline in these two age groups, respectively.

6.1.4.3 Secondary Efficacy Results

Secondary efficacy results are summarized based on the per-protocol population.

6.1.4.3.1 Effect of K85 on Total-C

With the exception of K85-95009, none of the Category 1 studies demonstrated a significant difference in mean or median percent change from baseline between the K85 4 g per day group and placebo in total-C. Patients in K85-95009 had mean and median reductions from baseline that was 13 and 10.1%, respectively. The range of median percent change from baseline for the K85 group overall was from -10.1% to +6.9%.

The pooled analysis of all Category 1 studies also did not show a significant relative change in total-C although absolute reductions were marginally significant.

Table 16. Total-C Efficacy in Pooled Population

	K85 4g n=206	Placebo n=204	p-value
Baseline value, mg/dL	284.3	285.4	
Endpt value, mg/dL	271.5	282.7	
Absolute chg, mg/dL	-12.8	-2.8	0.0218
Relative chg (%)	-2.9	-0.5	0.1096

obtained from Table 29, section 4.5.1 from NDA volume 151

Subgroup analyses by dyslipidemia type demonstrated significant reductions in total-C only in patients with Type V dyslipidemia.

Table 17. Total-C Efficacy by Dyslipidemic Classification

	K85 4 g	Placebo	p-value
Type IIb Dyslipidemia			
	n=111	n=118	
Mean baseline TC, mg/dL	298.3	296.8	
Mean endpoint TC, mg/dl	290.5	292.3	0.6426
Mean % chg	-2.3	-1.5	
Type IV/V Dyslipidemia			
	n=90	n=77	
Mean baseline TC, mg/dL	264.8	264.3	
Mean endpoint TC, mg/dl	247.4	264.6	0.0782
Mean % chg	-3.1	+0.9	
Type IV Dyslipidemia			
	n=65	n=54	
Mean baseline TC, mg/dL	238.4	233.8	
Mean endpoint TC, mg/dl	239.9	234.1	0.9918
Mean % chg	+2.0	+1.1	
Type V Dyslipidemia			
	n=25	n=23	0.0045

Mean baseline TC, mg/dL	333.7	335.7	
Mean endpoint TC, mg/dl	266.7	336.2	
Mean % chg	-16.5	+0.5	

6.1.4.3.2 Effect of K85 on HDL-C

K85 4 g was associated with an increase in HDL-C in all Category 1 studies but significant increases were observed in only two of the studies in which baseline HDL-C levels were the lowest. The following table summarizes the effect of K85 on HDL-C in the 8 pivotal studies.

Table 18. Changes in HDL-C in the PP population in Category 1 Studies

Study Number	n	median baseline HDL	mean % change from baseline	median % change from baseline	p-value*
CK85-014 K85 4 g placebo	48 46	40.5 40.5	+7.5 +5.8	0 +4	0.9576
CK85-017 K85 4 g placebo	24 23	39 35	+11.4 +2.4	+3.8 0	0.9066
CK85-019 K85 4 g placebo	26 26	33 32.5	+6.3 +3.6	+4.9 0	0.4753
CK85-022 K85 4 g placebo	28 30	39 38.5	+4.1 +3.4	-1.0 +3.9	0.8519
CK85-023 K85 4 g placebo	28 28	35 35	+5.9 +6.3	0 +8.8	0.4837
K85-94010 K85 4 g placebo	19 19	17 18	+13.9 -4.8	+5.9 -5.9	0.0354
K85-95009 K85 4 g placebo	20 19	26 27	+17.8 -0.9	+17.9 0	0.0081
CK85-013					ND

K85 4 g	12	28	+9.9	+10.7	
placebo	13	30	+9.6	+7.7	

*using a nonparametric approach (Wilcoxon two-sample test) comparing median values between treatment groups

The pooled analysis revealed a marginally significant increase in HDL-C from baseline relative to placebo (+8.9% vs +3.5%, respectively; p=0.0215). Again, significant increases occurred in the Type V patients who had the lowest baseline HDL-C.

Table 19. HDL-C Efficacy by Dyslipidemic Classification

	K85 4 g	Placebo	p-value
Type IIb Dyslipidemia			
	n=111	n=118	
Mean bsln HDL, mg/dL	39.0	37.3	0.6690
Mean endpt HDL, mg/dl	40.4	38.6	
Mean % chg	+5.5	+4.6	
Type IV/V Dyslipidemia			
	n=90	n=77	
Mean bsln HDL, mg/dL	29.5	30.5	0.0063
Mean endpt HDL, mg/dl	32.9	30.8	
Mean % chg	+13.1	+0.6	
Type IV Dyslipidemia			
	n=65	n=54	
Mean bsln HDL, mg/dL	32.4	32.9	0.1618
Mean endpt HDL, mg/dl	35.6	33.7	
Mean % chg	+11.1	+2.9	
Type V Dyslipidemia			
	n=25	n=23	
Mean bsln HDL, mg/dL	22.0	25.0	0.0019
Mean endpt HDL, mg/dl	25.8	24.0	
Mean % chg	+18.1	-4.6	

6.1.4.3.3 Effect of K85 on LDL-C

Calculated LDL-C levels increased significantly from baseline in the K85 treatment group relative to placebo. The range of the median percent change from baseline was -5.5% to 66.6% in the Category 1 studies. Results from the pooled analysis and subgroup analysis by dyslipidemic types are summarized in the following table.

Table 20. LDL-C Efficacy in Category 1 Studies

	K85 4 g		Placebo		p-value
	n	Mean Value	n	Mean Value	
Overall					
Baseline value, mg/dL	199	166.7	199	172.3	<0.0001
Relative chg, %	197	+16.8	191	+0.7	
Type IIb					
Baseline value, mg/dL	111	207.5	118	204.1	0.0099
Relative chg, %	110	+1.4	114	-3.9	
Type IV/V					
Baseline value, mg/dL	88	115.3	77	120.5	0.0020
Relative chg, %	87	+36.2	73	+7.8	
Type IV					
Baseline value, mg/dL	65	125.1	54	127.1	<0.0001
Relative chg, %	64	+33.8	50	+2.2	
Type V					
Baseline value, mg/dL	23	87.6	23	104.7	0.3840
Relative chg, %	23	+42.8	23	+19.9	

The applicant noted that while LDL-C increased in the K85 group, this increase was probably a result of the cholesterol enrichment of LDL particles associated with a shift from small, dense LDL particles to larger, more buoyant, and less atherogenic LDL particles. Particle size was not evaluated in these 8 pivotal studies.

The applicant also stated that, in general, mean baseline and endpoint LDL-C levels remained within the same NCEP ATP III category or were within the next successive category, and that Apo-B levels, a measure of atherogenic lipoproteins remained unchanged.

This reviewer requested additional analyses be performed to better characterize the increases in LDL-C. The applicant was asked to summarize the mean/median percent change in VLDL-C, apoB, and nonHDL in those patients treated with K85 4 g/day who had an increase in LDL-C and in those patients who had no increase in LDL-C. The data were provided for individual studies and the combined PP population. Not all studies had available data for these 3 lipoproteins. Only descriptive statistics are presented. No formal statistical analyses are performed as sample sizes are small within a subgroup and the subgroups are not derived from the randomized treatment groups.

Studies or analyses which evaluated changes in VLDL-C, demonstrated a reduction from baseline that paralleled the changes for the primary efficacy endpoint, Tg. This would suggest that the reduction in Tgs observed with K85 4 g/day reflected a reduction in Tg carried in VLDL-C lipoproteins. The reduction in VLDL-C appears to be more pronounced in the subgroup of patients who had an increase in LDL-C from baseline.

Overall, patients treated with K85 who had an increase in LDL-C from baseline also had mean increases in apoB lipoproteins and non-HDL-C whereas patients who had no increase in LDL-C

had mean reductions in these parameters. This finding was noted in the PP population (Table 21) and in each individual study (Table 22). This observation does not support the applicant's conclusion that increases in LDL-C associated with K85 therapy had neutral effects on other atherogenic lipoproteins or parameters (e.g., apoB lipoprotein, nonHDL-C).

Table 21. K85 4 g/day Treatment Group from PP population			
	VLDL-C	ApoB	Non-HDL-C
Subgroup w/ LDL increases			
n	64	101	133
mean relative chg	-33.1%	+7.18%	+1.8%
median relative chg	-37.2%	+4.66%	+1.8%
SD	26.87%	+16.6%	+23.14%
range	-78 to +79%	-36.3 to +51.3%	-135 to +130%
Subgroup w/ NO increase in LDL			
n	29	55	66
mean relative chg	-7.6%	-4.88%	-13.7%
median relative chg	-11.1%	-3.57%	-11.8%
SD	+34.8%	+9.74%	+12.27
range	-52 to 123%	-29.8 to +13.7%	-66 to +11%

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Table 22. Changes in VLDL-C, ApoB, and Non-HDL-C from Baseline in the K85 4g-treated patients who had INCREASES (↑ LDL) or NO increase (∅ LDL) in LDL-C from baseline

	CK85-013		CK85-014		CK85-017		CK85-019		CK85-022		CK85-023		K85-94010		K85-95009	
baseline Tg for K85 4 g group mean median	308.2 mg/dL 299 mg/dL		294.5 mg/dL 264.5 mg/dL		305.8 mg/dL 276 mg/dL		295.6 mg/dL 267.5 mg/dL		343.5 mg/dL 279 mg/dL		358.3 mg/dL 294.5 mg/dL		840.1 mg/dL 810.5 mg/dL		919 mg/dL 817.5 mg/dL	
n	↑ LDL	∅ LDL	↑ LDL	∅ LDL	↑ LDL	∅ LDL	↑ LDL	∅ LDL	↑ LDL	∅ LDL	↑ LDL	∅ LDL	↑ LDL	∅ LDL	↑ LDL	∅ LDL
	11	1	29	17	18	5	18	8	16	12	10	14	13	6	17	3
relative chg (%) in VLDL- C mean median	ND	ND	ND	ND	ND	ND	-25.8 -26.9	-17.1 -20.4	-27.5 -30.8	-13.6 -16.2	ND	ND	-30.4 -35.2	-22.2 -15.7	-48.2 -49.5	+70.7 +50.5
relative chg (%) in apoB mean median	+8.28 +9.09	-13.75 -13.75	+9.573 +4.0	-3.459 -0.917	ND	ND	+4.50 +2.724	-3.04 0	+8.53 +5.22	-8.37 -6.51	+9.04 +4.52	-4.36 -3.69	ND	ND	+2.86 +0.781	-3.27 -3.36
relative chg (%) in non- HDL-C mean median	+5.1 +4.36	-39.2 -39.2	+9.0 +7.1	-11.5 -12.6	+7.5 +4.7	-30.5 -25.3	+2.6 -0.2	-8.9 -9.8	+8.2 +2.7	-13.4 -14.5	+8.2 +2.7	-13.4 -14.5	-7.3 -6.5	-24.9 -26.1	-18.9 -15.5	-1.2 -2.1

Assessment of CHD risk can also evaluate the ratio of atherogenic to non-atherogenic lipoproteins. Such ratios include TC/HDL-C, LDL-C/HDL-C, and apoB/HDL-C. This applicant was asked to further analyze the Category 1 studies for changes in LDL-C/HDL-C from baseline. The purpose of this analysis was to assess whether the increases in LDL-C and HDL-C while on K85 therapy altered the ratio of these two lipoproteins in an unfavorable direction (i.e., increase from baseline).

The following table summarizes the LDL-C/HDL-C for the overall PP population and by dyslipidemic patient groups.

Table 23. Changes in LDL-C/HDL-C from Baseline in Category 1 Studies

	K85 4 g	Placebo	P-value ^a
Overall			
	n=197	n=191	
Baseline ratio	5.1	5.2	
Endpoint ratio	5.3	5.0	
Absolute change	0.26	-0.22	0.0042
Relative change (%)	11.79	0.50	0.0197
Type IIb Hyperlipidemia			
	n=110	n=114	
Baseline ratio	5.7	5.8	
Endpoint ratio	5.5	5.4	
Absolute change	-0.15	-0.41	0.1457
Relative change (%)	0.11	-5.70	0.0993
Type IV/V Hyperlipidemia			
	n=87	n=73	
Baseline ratio	4.3	4.3	
Endpoint ratio	5.1	4.4	
Absolute change	0.79	0.13	0.0327
Relative change (%)	26.57	10.94	0.1324
Type IV Hyperlipidemia			
	n=64	n=50	
Baseline ratio	4.2	4.1	
Endpoint ratio	5.1	4.2	
Absolute change	0.95	0.08	0.0023
Relative change (%)	27.89	0.56	0.0004
Type V Hyperlipidemia			
	n=23	n=23	
Baseline ratio	4.7	4.7	
Endpoint ratio	5.0	5.0	
Absolute change	0.33	0.24	0.9145
Relative change (%)	22.89	33.50	0.7311

*In a few instances subjects were excluded from Baseline ratios to maintain a consistent sample size for each set of four values.

^aP-values were computed using analysis of variance (ANOVA).

K85 therapy did not reduce the LDL to HDL ratio from baseline. The difference in effect was significantly different from that of placebo in the overall population and Type IV patients. For

patients with Type V dyslipidemia, while there was a 23% increase in this ratio, a similar increase was noted in the placebo group such that this change was not significantly different.

Other atherogenic lipid biomarkers include non-HDL and apoB lipoproteins. The following table summarizes the effect of treatment non-HDL levels.

Table 24. Changes on non-HDL-C in PP population

	K85		Placebo		p-value
	n	mean value	n	mean value	
Overall	205	-3.9%	204	-1.0%	0.1046
Type IIb	111	-3.2%	118	-2.1%	0.6072
Type IV	65	+1.4%	54	+1.0%	0.8932
Type V	25	-18.9%	23	+0.7%	0.0022

There were no significant differences in non-HDL changes between K85 and placebo except for the Type V patients. This patient population had a significant reduction in non-HDL-C levels.

ApoB lipoproteins were not measured in all studies and was not analyzed in the ISE. In the 6 studies which had data, there were no significant differences in mean percent changes from baseline in apo B levels between K85 and placebo groups; however, there was an increase in mean levels of apo B lipoproteins in the K85 group in 5 out of the 6 studies.

6.1.4.3.4 Effect of K85 on VLDL-C

Four Category 1 studies measured VLDL-C levels and contributed to the PP population for this secondary efficacy measure. The following table summarizes the mean change from baseline in VLDL-C in the PP population and by dyslipidemia type. Overall, K85 4 g significantly reduced VLDL-C from baseline relative to placebo with the effects consistent across dyslipidemia type.

Table 25. VLDL-C Efficacy

	K85	Placebo	p-value
Overall			
	n=93	n=94	
baseline, mg/dL	109.8	101.2	<0.0001
relative chg (%)	-25.2	+8.0	<0.0001
Type IIb			
	n=34	n=39	
baseline, mg/dL	49.5	58.9	0.0246
relative chg (%)	-10.9	+13.7	0.0213
Type IV/V			
	n=59	n=54	

baseline, mg/dL	144.6	133.1	<0.0001
relative chg (%)	-33.3	+4.8	<0.0001
Type IV			
	n=36	n=31	
baseline, mg/dL	95.3	79.1	<0.0001
relative chg (%)	-34.3	+6.7	0.0003
Type V			
	n=23	n=23	
baseline, mg/dL	221.8	206.0	0.0002
relative chg (%)	-31.9	+2.2	0.0004

6.1.4.4 Co-administration with Statins

The applicant submitted 5 sources of data supporting efficacy and safety of K85 co-administered with statins. Only one of these sources contained CRFs and data listings. Study K85-95014 (volume 127) was a category 2 study comparing K85 4 g per day in combination with simvastatin to simvastatin monotherapy in patients with Type IIb dyslipidemia. The remaining sources of data came from category 4 studies and were not reviewed due to unavailable data listings and CRFs.

In K85-95014, male or female patients with established CHD were eligible if they had a Tg level ≥ 204 mg/dL and did not have any of the listed exclusion criteria including treatment with another statin within the last 6 weeks. Eligible patients with a total-C > 232 mg/dL and Tg > 265 mg/dL received simvastatin daily for 6 weeks during a dietary run-in period. At the end of this run-in period, 30 subjects were randomized to receive K85 4 g per day with simvastatin and 29 subjects were randomized to receive placebo with simvastatin (simvastatin monotherapy group) for 24 weeks. The simvastatin dose was determined individually by the investigator. The primary efficacy endpoint was the change from baseline to end of treatment period in serum Tg levels. Efficacy analyses were similar to those described for the Category 1 studies.

Efficacy results are summarized in the following table.

Table 26. Combination with Simvastatin Efficacy Results

Efficacy Endpoint	K85 + simva (N=25) (Median %)	Simva (N=21) (Median %)	p-value*
Primary Efficacy Endpoint			
Change in Tg	-28.9	0.0	0.0012
Secondary Efficacy Endpoint			

Change in TC	-3.1	+1.8	0.0382
Change in HDL-C	0.0	+8.8	0.0425
Change in LDL-C	0.0	+8.1	0.7491
Change in VLDL-C	-47.8	-26.7	0.1098
Change in ApoB	-1.980	+1.439	0.0392
Change in nonHDL-C	-7.7	+0.5	0.1581

The patients who received K85 with simvastatin achieved a 29% reduction in Tg from baseline compared to no change in the simvastatin monotherapy group. Baseline values were obtained after the dietary run-in period while on simvastatin therapy.

Although this study suggests K85 coadministration with simvastatin provides further Tg-lowering than continued simvastatin monotherapy, results from this single small study are inadequate to support a proposed labeling indication for combination therapy with all statins. This study did not evaluate efficacy based on a specified dose of simvastatin. The dose of simvastatin was selected by the investigator with the majority of subjects treated with simvastatin 20 mg daily without adjustment during the double-blind period.³ Based on the simvastatin label, patients with mixed dyslipidemia achieved Tg-reductions ranging from -12 to -33% with simvastatin 5 mg to 80 mg. It is conceivable that a similarly designed study using only the 40 or 80 mg dose of simvastatin would result in no significant difference in Tg-lowering between combined K85/simvastatin therapy and simvastatin monotherapy. This study design also does not allow for a comparison between the combination therapy and K85 monotherapy to determine what effect simvastatin adds to the combination therapy.

Finally, it does not appear that the conduct of this study reflects current guidelines for the treatment of Type IIb dyslipidemia. Based on the demographics of these patients, current NCEP guidelines would recommend that LDL-C levels be treated to < 100 mg/dL (for patients with established CHD or CHD risk equivalents). The mean baseline LDL-C levels were 128.7 mg/dL and 164.1 mg/dL for the K85/simvastatin and simvastatin monotherapy groups, respectively. Mean LDL-C levels at the end of study remained essentially unchanged. It is, therefore, reasonable to assume that inadequate statin dosing was selected in this study for LDL-C and Tg-lowering. Furthermore, the conduct of this study does not provide information on how these two products might be used in clinical practice.

Based on the results of the Category 1 studies, K85 does appear effective at lowering Tg levels across different dyslipidemic populations. However, the notable increase in LDL-C for the IIb and IV dyslipidemics precludes its use as first-line therapy in these patients who have elevations in both LDL-C and Tg levels. Indeed, such increases observed with K85 therapy will likely require its co-administration with an effective LDL-lowering agent. An adequately designed trial is therefore necessary to investigate the effects of combination therapy. Such a study should

³ 10 patients in each group received simvastatin 40 mg, 20 patients in the combination group and 17 patients in the simvastatin group received 20 mg, and 2 patients in the simvastatin group received 10 mg – volume 128, Section 7.2

include treating patients LDL-C levels to recommended goals followed by the addition of K85 to address elevated Tg levels as a secondary target of therapy.

6.1.4.4 Comparative Efficacy to Gemfibrozil

As discussed in Section 2.2 of the review, gemfibrozil is a fibric-acid derivative which has an indication to lower Tg levels in patients with Types IIb, IV, and V dyslipidemia. The applicant provided data from Protocol K85-95011 (volumes 120 and 121) which was a double-blind study comparing K85 4 g per day to gemfibrozil in patients with severe hypertriglyceridemia. This study was classified under the Category 2 studies and the results were not presented in the proposed label; however, the results of this trial are worthy of discussion given the difference in lipid-altering effects achieved with the two agents and the results of a substudy.

After 6 weeks of dietary intervention, eligible patients were randomized to 12 weeks of treatment with K85 4 g per day or gemfibrozil 1200 mg per day. Patients had to have a Tg level > 398.6 mg/dL at Weeks -6 and -2 of the screening period. The primary efficacy endpoint was the change from baseline to the end of study in serum Tg levels. Efficacy analyses were similar to those described for the Category 1 studies.

Forty-nine patients were randomized to each of the two treatment groups. The mean age of the cohort was 49 years. Approximately 90% of the patients were male and all were Caucasian. The mean baseline Tg level was 1040.5 mg/dL in the K85 group compared to 1013.5 mg/dL in the gemfibrozil group. The median value was 779 mg/dL in both groups. The following table summarizes the primary and secondary efficacy results in the PP population.

Table 27. Comparative Efficacy with Gemfibrozil

Efficacy Endpoint	K85 (N=41) (Median %)	Gemfibrozil (N=42) (Median %)	p-value*
Primary Efficacy Endpoint			
Change in Tg	-35.8	-60.0	0.0002
Secondary Efficacy Endpoint			
Change in TC	-7.5	-12.0	0.2949
Change in HDL-C	+2.9	+19.9	0.0012
Change in LDL-C	+6.6	+1.9	0.8529
Change in VLDL-C	-26.1	-28.3	0.5475
Change in ApoB	+11.977	+11.454	0.9944
Change in nonHDL-C	-7.8	-15.2	0.1099

*nonparametric p-values using Wilcoxon two-sample tests to evaluate the overall treatment effect between groups

Gemfibrozil achieved a greater reduction in Tg and increased HDL-C to a larger extent than K85 therapy. There was no statistical difference between the two treatment groups for the other efficacy parameters.

A substudy evaluating LDL particle size and LDL oxidizability was conducted in this cohort.⁴ The published results were submitted with this application and referred to by the applicant as evidence that increases in LDL-C associated with K85 therapy reflect a favorable shift from atherogenic, small dense LDL particles to the less atherogenic, larger LDL particles. This substudy performed analyses of samples obtained from 28 of the 98 patients enrolled in the study. These analyses included evaluating LDL subfractions and oxidation lag time, rate, and diene formation before and after treatment. The results of this study showed that for both treatments, the main LDL subfractions at baseline were the small and dense ones represented by LDL3 and LDL4. After therapy with either K845 or gemfibrozil, an increase in the more buoyant LDL particles (LDL1 and LDL2) was noted. Oxidizability studies suggested that after K85 therapy, LDL was more prone to oxidation (decreased lag time) whereas no significant change in LDL oxidizability was noted with gemfibrozil. Oxidative modification of LDL has been implicated in the initiation of atherosclerosis. The authors concluded that the clinical relevance of these findings is not known.

More treatment-emergent AEs occurred in the gemfibrozil group (22.4%) compared to the K85 group (14.3%). Similarly, there was a higher incidence of SAEs in the gemfibrozil group (6.1%) compared to the K85 group (2.0%). One death occurred in a gemfibrozil-treated patient who experienced a myocardial infarction approximately 1 month after initiating treatment. The patient was a 68-year old patient who had had 3 previous MIs. One patient in the K85 group discontinued therapy due to pancreatitis. The patient enrolled in the trial with a Tg of 3766 mg/dL and received treatment for 1.5 months when she was hospitalized for pancreatitis. No follow-up Tgs were available. The most common AEs reported in the K85 group were abdominal pain (2.4%) and diarrhea (2.1%).

In conclusion, this comparative efficacy study demonstrates greater TG-lowering and HDL-raising efficacy of gemfibrozil over K85. Both products increase LDL-C and analyses of plasma samples from a subgroup of study subjects associated this increase with an increase in LDL subfractions that are of the less atherogenic form. Conflicting results from a separate analysis of LDL oxidizability were noted for the K85 group whose sample had a greater tendency for LDL oxidation. Except for one patient in who developed pancreatitis while on K85, the safety profile from this study was similar to the Category 1 studies (see Section 7.0).

⁴ Sebastian JH et al. The effect of concentrated n-3 fatty acids versus gemfibrozil on plasma lipoproteins, low density lipoprotein heterogeneity and oxidizability in patients with hypertriglyceridemia. *Atherosclerosis*. 2000; 153: 129-138.

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6.1.5 Efficacy Conclusions

K85 4 g/day effectively lowered Tg levels from baseline relative to placebo. The degree of Tg-lowering was variable with a greater reduction achieved in patients with more severe hypertriglyceridemia. Reductions in VLDL-C paralleled the changes in Tg.

K85 4 g/day had minimal effect on total-C and HDL-C although patients with Type V dyslipidemia with baseline HDL-C < 25 mg/dL had significant increases in HDL-C while on K85 therapy.

Significant increases in LDL-C associated with K85 treatment were consistently observed regardless of baseline dyslipidemia type. The type V hypertriglyceridemic population had the greatest mean percent increases in LDL-C from baseline; however, this change was not significantly different from placebo. Evaluation of other atherogenic lipid biomarkers included change in non-HDL-C, apo B, and LDL/HDL-C. Only the Type V patient population demonstrated significant reductions in non-HDL-C levels. Although there were no significant differences in the change in apoB levels between K85 and placebo, 5 out of 6 studies with these data revealed an increase in apoB levels in the K85 group. Finally, significant increases in LDL/HDL ratios were observed in the overall population and Type IV patients. A marginally significant increase in the ratio was observed in the Type IIb patient population.

In conclusion, while K85 is an effective Tg-lowering agent, subgroup analyses by dyslipidemic classification demonstrated more favorable lipid-altering in the Type V dyslipidemic population whose primary lipid derangement was Tg elevation. These patients achieved significantly greater reductions in Tg, TC, VLDL-C, and non-HDL-C and significantly greater increases in HDL-C levels. Although percent LDL-C increase was higher in this subgroup, the increase was not statistically different from placebo. In contrast, patients with Types IIb and IV dyslipidemia had less of a reduction in Tg and VLDL-C, and achieved no statistical difference in TC, HDL-C, and non-HDL-C relative to placebo. The following table summarizes the median changes in lipid parameters from baseline in patients with Types IIb, IV, and V dyslipidemia.

Table 28. Summary of Median Percent Changes from Baseline for Lipid Parameters by Dyslipidemic Classification

	TG		TC		HDL		LDL		VLDL		nonHDL	
	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo	K85	Pbo
Type IIb	-26.3	+2.9	-2.3	-1.5	+5.5	+4.6	+1.4	-3.9	-10.9	+13.7	-3.2	-2.1
Type IV	-25.5	+4.5	+2.0	+1.1	+11.1	+2.9	+33.8	+2.2	-34.3	+6.7	+1.4	+1.0
Type V	-39.4	+2.8	-16.5	+0.5	+18.1	-4.6	+42.8	+19.9	-31.9	+2.2	-18.9	+0.7

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

Twenty-three studies for hypertriglyceridemia in which CRFs were available were included in the integrated analyses of safety. The following populations were defined for analyses:

All subjects from Category 1 Studies – This population consisted of subjects from the double-blind, parallel, placebo-controlled studies. A total of 454 patients were evaluated in this dataset (K85 4 g = 226 and placebo = 228).

All subjects who received K85 – This population consisted of all subjects who received K85 at any dose level from the double-blind, parallel, placebo-controlled studies for hypertriglyceridemia. Subjects who received K85 at multiple dose levels were counted only once. 665 patients treated with K85 were evaluated in this dataset.

All subjects population – This population consisted of all subjects who received study medication, K85 at each dose level or placebo from the Category 1-3 studies. Subjects who received K85 at multiple dose levels were counted in each appropriate dose level. While data from this subject population included several doses of K85, there were too few patients in the 6 and 8 g dose groups to adequately assess safety beyond the 4 g dose or to definitively comment on dose-response.

7.1.1 Deaths

There were a total of 5 deaths in the integrated analyses of safety. Three occurred in the K85 4 g dose group, 1 in the K85 6 g dose group, and 1 in placebo.

Subject 006.125 – K85 4 g/day

This was a 62 yo male with a history of type 2 dyslipidemia, HTN, CABG x 2, and 3 MIs. He began treatment with K85 4 g/day on 1-30-91 and took his last medication on 4-24-91 and completed the study. On 2/15/91 the patient collapsed and died. Post mortem findings included moderate MI, atherosclerosis of arteries in the circle of Willis, congested and edematous lungs, patent pulmonary arteries, and fibrous pericarditis. Concomitant medications included atenolol and nifedipine. Because no information regarding the relationship of event and drug was recorded in the CRF, this event was recorded as related to study drug.

Comment: Given the extensive h/o CAD and that the event took place 16 days after the last dose of medication, causality of event to drug is questionable.

Subject 001.040 – Placebo

This was a 69 yo male with a history of brain stem attacks, arthritis, difficulty with micturition requiring cystoscopy, and angina who began treatment with placebo on 5-7-91. On 5/15/91 the

patient was admitted with chest pain and diagnosed with acute IWMI. Study medication was discontinued and streptokinase was administered. On 1/11/91 he went into Vfib that did not respond to defibrillation. The patient expired.

Subject 001.019 – K85 6g/day

This was a 40 yo male with no other significant medical history who began therapy with K85 6 g/day on 5-2-90. On 1/11/91, the subject committed suicide. No further information was available.

Subject 001-023 – K85 8g/day

This was a 52 yo female who began treatment w/ K85 8g/day on 10-11-90 then reduced to K85 4g/day on 5-15-91. On 1/11/91, she died of an apparent MI.

7.1.2 Other Serious Adverse Events

The incidence of SAEs across all K85 doses was 1.7% (2 g), 0.5% (3 g), 3% (4 g), 4.8% (6 g), 0 (8 g), and 1.6% (placebo). Only two cases were considered possibly related to study drug.

Subject 001.001 – extensive colitis

This was a 73 yo female with a history of HTN, b/l knee replacement, and DVT who began treatment with placebo on 12-7-95 then was switched to K85 2 g/day on 4-4-96. On 1/11/91 she developed lower GI bleeding and a colonoscopy revealed multiple ulcerations throughout the colon. Biopsy revealed ischemic colitis. Therapy was discontinued and the patient withdrew from the study on 5-2-96. The investigator considered the event possibly related to study drug. However, it should be noted that the patient's age and past medical h/o may also predispose to this condition.

Subject 001.024 – Arrhythmia, flu syndrome and dyspnea

This was a 65 yo male with a history of MI and DVT who received placebo initially then began K85 4g/day after enrolling in an extension study. On 1/11/91 he had flu-like symptoms, dyspnea, and muscle pains. CK level was 176 umol/L and the calcium was low (no level recorded). On 1/11/91 the patient was admitted with a serious cardiac arrhythmia, diagnosed as Vfib and cardiac insufficiency after a myocardial infarction. Pacemaker was implanted.

7.1.3 Dropouts and Other Significant Adverse Events

The incidence of dropouts due to AEs was 3.5% in the K85 group versus 2.6% in the placebo group in the Category 1 studies. The majority of these events were GI-related.

7.1.4 Common Adverse Events

The most common adverse events experienced by the K85 4 g per day group in the placebo-controlled studies (Category 1) were eructation (4.9%) and infection (4.4%). While these

incidences were higher than in the placebo group, the differences were not statistically significant.

The only adverse event that occurred at a significantly higher rate in K85 4 g group compared to placebo was taste perversion (primarily “fishy taste”) with an incidence of 2.7% in the treatment group versus none in the placebo group (p=0.0147)

7.1.7 Laboratory Findings

Laboratory tests included hemoglobin, WBC, platelet counts, AST, ALT, and serum creatinine. Actual lab values at baseline and throughout the study were collected and summarized in the individual study reports as patient line listings. Data were also analyzed as shifts from baseline to end of study based on the National Cancer Institute Common Toxicity Criteria (Version 2). This was summarized in the integrated analysis of safety and the applicant concluded that , in general, shifts in toxicity grade were from 0 to 1 or increased by only 1 grade level but never exceeded toxicity grade 2. This reviewer evaluated the individual hematology and biochemistry data (Supplemental tables 16.2.15 and 16.2.16 located in each study report) for the placebo-controlled studies and did not identify any clinically relevant changes in laboratory values.

7.1.8 Vital Signs and ECGs

Vital signs were reported in the individual study reports. Some reductions in BP were noted in the K85 groups but these changes were not consistent across the different studies.

ECGs were not collected for safety monitoring in these studies.

7.1.9 Safety by Disease Indication

Adverse experience data were evaluated by dyslipidemia types IIB, IV, and V. The following table summarizes the incidence of AEs by body system and dyslipidemia type.

Table 29. Incidence of AEs (%) by Dyslipidemia Type

Body System	K85			Placebo		
	IIB n=276	IV n=195	V n=108	IIB n=187	IV n=108	V n=49
at least 1 AE	35.9	25.6	21.3	24.1	16.8	14.3
body as whole	11.2	9.2	6.5	10.2	7.5	6.1
CV	2.9	2.6	4.6	1.1	1.9	2.0
GI	19.6	11.3	8.3	12.8	9.3	8.2
Metabolic-nutritional	0.4	1.0	0.9	0.5	0	2.0
Musculoskeletal	2.5	1.0	0	1.6	0	0

Respiratory	2.5	2.6	2.8	0.5	0.5	4.1
Skin	1.8	2.6	0	1.1	1.9	0
Special Senses	5.1	3.6	0	1.1	0	0
Urogenital	0.4	0.5	0.9	0	0	2.0

Overall, the rates of AEs were higher in the K85 treatment group than placebo across the different dyslipidemic populations; however, the majority of AEs were GI-related. Of these, eructation, dyspepsia, nausea, and diarrhea were most commonly reported as preferred terms.

The incidence of CV AEs was numerically higher in the K85 group compared to placebo. This difference may reflect the longer treatment duration of the K85 group compared to placebo as Table 29 included patients in Categories 1, 2, and 3. These studies included open-label, extension periods for the K85 group with treatment duration as long as 91 weeks. In contrast, the data from the placebo group were primarily derived from the Category 1 studies and treatment duration was only out to a maximum of 21 weeks.

Review of the AE line listings for the 8 pivotal clinical studies where treatment duration was similar (but limited to a maximum of 16 weeks) between K85 4 g (5.8%) and placebo revealed similar CV adverse event rates (5.3%).

7.1.10 Withdrawal Phenomena and/or Abuse Potential

There is no evidence that this product has abuse potential or withdrawal potential.

7.1.14 Safety by Gender

Males and females treated with K85 experienced more AEs than their counterparts treated with placebo. The most common AEs reported were GI-related.

Table 30. Incidence of AEs (%) by Gender

Body System	K85		Placebo	
	Male n=471	Female n=184	Male n=274	Female n=96
w/ at least 1 AE	27.2	36.4	19.3	21.9
Body as whole	8.3	12.5	6.9	12.5
CV	3.0	3.3	1.5	2.1
GI	13.4	19.0	10.9	10.4
Metabolic-nutrition	0.2	1.6	1.1	0

Respiratory	1.9	4.9	1.5	0
Skin	1.5	1.6	0.4	4.2
Special Senses	4.2	4.3	0.4	1.0
Urogenital	0.4	0.5	0	1.0

7.1.15 Safety by Age

Adverse experiences by age < 60 years and ≥ 60 years were evaluated and similar results were observed. A higher rate of AEs were reported in both age categories in the K85 group versus placebo with the majority of events being GI-related.

Table 31. Incidence (%) of AEs by Age < 60 years and ≥ 60 years

Body System	K85		Placebo	
	< 60 yrs n=403	≥ 60 yrs n=117	< 60 yrs n=228	≥ 60 yrs n=75
w/ at least 1 AE	28.8	35	22.8	22.7
Body as whole	11.4	8.5	10.1	8.0
CV	3.2	6.0	1.8	2.7
GI	13.6	17.1	12.7	9.3
Metabolic-nutrition	0.7	0.9	0.9	1.3
Respiratory	3.5	2.6	1.8	0
Skin	1.5	2.6	0.9	2.7
Special Senses	1.5	1.7	0	1.3

7.1.16 Overdose Experience

No data provided.

7.2 Adequacy of Patient Exposure and Safety Assessments

7.2.1 Description of Primary Clinical Data Sources (Populations Exposed and Extent of Exposure) Used to Evaluate Safety

7.2.1.1 Demographics

From the All-Subjects Population dataset, there were no significant differences across all K85 dose groups and placebo with respect to age, gender, race, height, weight, or BMI at baseline. Although there was more variability for baseline lipid parameters, none of these differences reached statistical significance.

7.2.1.2 Extent of exposure (dose/duration)

The following table summarizes the extent of exposure by dose and duration from the all-subject population:

Table 32. Treatment Exposure

Duration of treatment (wks)	K85 2 g n=115	K85 3 g n=198	K85 4 g n=395	K85 6 g n=21	K85 8 g n=18	Placebo n=370
mean	10	6.8	23.6	16.1	8.2	10.4
median	5.1	4.4	13.0	16.6	8.1	12.1
SD	9.03	3.83	21.12	3.13	0.88	4.21
range	0-28	1-14	0-91	8-23	5-9	0-21

Within each dose group, the majority of patients received therapy for 20 weeks or less. Approximately 35% of the K85 4 g per day group received therapy beyond 16 weeks. The extent of exposure at doses above 4 g per day was limited.

7.2.2 Postmarketing Experience

Omega-3-fatty acids, including DHA and EPA, are available in the U.S. as dietary supplements. Omacor® has been available in numerous foreign countries for different indications as early as 1994. This product has marketing approval for hypertriglyceridemia in 14 countries (Norway, France, Austria, Germany, Greece, UK, Philippines, Thailand, Spain, Portugal, Ireland, Belgium, Holland, and Luxemburg).

No approved marketing application has been withdrawn due to safety or efficacy concerns and no marketing application has been denied due to safety concerns. The applicant reports that no spontaneous reports of AEs or SAEs have been reported to Pronova Biocare and /or its licensees between January 1, 1994 and September 1, 2002.

7.2.2.3 Pregnancy Category Labeling

Pharmacology-toxicology recommends Pregnancy Category C labeling. The 2-year carcinogenic studies in rats and mice were considered inadequate; however, no additional studies were required by ECAC (see Pharm/tox review).

7.2.9 Additional Submissions, Including Safety Update

The 4-month safety update was submitted May 24, 2004. This submission summarized preliminary safety data for 5 ongoing clinical trials and provided a publication from February 2004 of a study using K85 4 g per day in patients with IgA nephropathy. The applicant obtained safety update information from the manufacturer, Pronova, who also stated that no foreign regulatory authority has reported any major changes in the marketing status or labeling information for Omacor®.

To date, 1,473 patients have enrolled in these 5 clinical studies. The doses studied in these trials are K85 1 to 2 grams per day. The studies are being conducted in a patient population at risk for CV clinical events. Primary endpoints are clinical endpoints or prevention of arrhythmias in post-MI patients; Tg-lowering is not an efficacy measure. Preliminary safety results for these 5 studies do not reveal any new findings from the initial data submitted to NDA 21-654.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The proposed dosing regimen is Omacor 4 g per day as a single 4 g dose or two 2-g doses. Omacor capsules are supplied as 1 gm soft-gelatin capsules. No food effect studies were conducted; however, Omacor was administered with meals in the clinical trials and the label should recommend that it be given with meals to achieve similar efficacy as observed in the clinical studies.

Dose-response was evaluated in a pooled analysis of all Category 1 studies and 4 Category 2 studies. The effect of Tg-lowering by K85 dose of 2, 3, 4, 6, and 8 g per day are summarized in the following table:

Table 34. Efficacy by Dose

	K85 - 2g n=75	K85 - 3 g n=61	K85 - 4 g n=206	K85 - 6 g n=18	K85 - 8g n=6	Placebo
Baseline median Tg, mg/dL	293.2	757.1	422.8	587.1	251.5	412.0
Mean % chg from baseline	-4.2	-20.4	-28.0	-30.5	-44.5	+1.4

Median % chg from baseline	-12.2	-24.9	-31.2	-28.9	-43.2	-3.0
p-value	0.9947	0.0007	<0.0001	0.0027	0.0192	---

Although significant reductions were not observed in all doses evaluated, increasing Tg-lowering was observed with increasing doses of K85. Significant reductions were noted with doses as low as 3 g per day.

Prospective clinical studies have suggested a cardioprotective effect associated with K85 therapy; however, the doses evaluated were lower than 4 g daily. In the GISSI-Prevenzion Trial, the dose evaluated was 1 gram daily. The applicant should evaluate lipid-altering effects at these lower doses in larger studies to determine if significant Tg-lowering can be achieved at the lower dose without increasing LDL-C levels.

8.4 Pediatrics

The sponsor requested a full waiver for pediatric study requirements citing that familial hypertriglyceridemia is a rare condition in pediatric patients. The small number of patients limits the ability to conduct adequate and well-controlled studies.

8.5 Advisory Committee Meeting

not applicable

8.6 Literature Review

The applicant submitted several published articles evaluating the effects of omega-3-fatty acids on blood pressure, platelets, coagulation, and several non-cardiovascular disease processes (e.g., Crohn's, atopic dermatitis, psoriasis). No datasets or CRTs were available for these published studies. Two publications merit discussion in this review: the GISSI-Prevenzione Trial and a study of high dose omega-3-FA in post-MI patients.

GISSI-Prevenzione Trial⁵

This study was a large, open-label trial in patients with a recent myocardial infarction (≤ 3 months). The trial was initiated in October 1993 at several medical centers in Italy. 11,324 patients were randomly allocated to treatment with an omega-3-FA 1-gram daily (n=2836), 300 mg vitamin E (n=2830), omega-3-FA plus vitamin E (n=2830), or placebo (n=2828). The primary combined efficacy endpoints were: the cumulative rate of all-cause death, nonfatal MI, and nonfatal stroke; and the cumulative rate of CV death, nonfatal MI, and nonfatal stroke.

⁵ GISSI-Prevenzione Investigators. Dietary supplementation with n-3 polyunsaturated fatty acids and vitamin E after myocardial infarction: results of the GISSI-Prevenzione trial. *Lancet* 1989;2:757-761.

Secondary analyses were performed on the individual components of the primary endpoint and the main causes of death.

Analyses included a two-way analysis comparing efficacy of omega-3-FA supplements to no omega-3-FA supplements and vitamin E supplements to no vitamin E supplements. A 4-way analysis was also performed which compared the omega-3-FA, vitamin E supplements, and combined treated with control as well as the combined treatment with individual interventions.

Therapy with omega-3-FA resulted in a 10% relative risk reduction for the combined endpoints of death, nonfatal MI, and nonfatal stroke, compared to controls in the 2-way analysis that was marginally significant at $p=0.048$. The 4-way analysis had a slightly better risk reduction of 15%. No significant risk reduction was observed for the combined endpoint of cardiovascular death, nonfatal MI, and nonfatal stroke in the 2-way analysis.

The authors reported no clinically important changes for cholesterol (total, HDL, and LDL) in any of the treatment groups. They also acknowledged that this trial was initiated prior to a clinical benefit was established for statin therapy in post-MI patients.

While a risk reduction associated with omega-3-FA was noted in this prospectively conducted clinical study, the degree of reduction is modest and of marginal significance. In contrast, clinical outcome studies involving statins in similar patient populations have demonstrated relative risk reductions of 20-30%. Furthermore, the trend towards a clinical benefit in the GISSI-Prevenzione Trial cannot be interpreted as an expected clinical benefit with Omacor® 4 gram per day. This clinical trial used a lower dose of omega-3-FA and did not show an effect on lipids. In fact, the absence of an increase in cholesterol levels in the GISSI-Prevenzion trial might suggest that therapy with higher amounts of omega-3-FAs, which unfavorably affect cholesterol levels, may result in no clinical benefit.

High Dose Omega-3-FA in Post-MI Patients

This was a randomized, placebo (corn oil) controlled, double-blind study in patients who had just experienced an acute MI⁶. Three hundred patients were randomized to Omacor® 4 gram per day or corn oil between the fourth and eighth day after the MI. The objective of this study was to determine what effect Omacor® would have on subsequent cardiac events and the lipid profile. Patients were followed for a median time of 1.5 years. Cardiac events included cardiac death, resuscitation, recurrent MI, unstable angina, and revascularization procedures. Death from other causes were also recorded. Significant reductions in Tg levels and significant increases in HDL levels were observed in the Omacor® group compared to placebo. No significant difference in rate of cardiac events was observed between the two treatment groups. A total of 42 (28%) of patients in the Omacor® group and 36 (24%) patients in the placebo group experienced at least one cardiac event.

The applicant has included the following statements in the proposed labeling:

⁶ Nilsen D et al. Effects of a high-dose concentrate of n-3 fatty acids or corn oil introduced early after an acute myocardial infarction on serum triacylglycerol and HDL cholesterol. *Am J Clin Nutr* 2001;74:50-56.

Treatment with Omacor® at various dose levels was associated not only with reduced TG levels but also with reduced risk of various cardiovascular events, including hypertension (systolic, diastolic, and mean arterial blood pressures),^{i,ii,iii,iv,v} incidence of vein graft occlusion after undergoing artery bypass grafting,^{vi} progression of coronary atherosclerosis,^{vii} coronary mortality, cardiovascular death, sudden death, fatal and nonfatal coronary events, and a combined endpoint of death, nonfatal MI, or stroke.

Given the inconsistent results of clinical trials evaluating the clinical CV benefits of omega-3-fatty acids, no indication or implied claims of clinical benefit associated with Omacor® should be allowed in labeling.

8.7 Postmarketing Risk Management Plan

none proposed

9 OVERALL ASSESSMENT

9.1 Conclusions

Omacor® 4 grams daily is an effective Tg-lowering agent for Types IIb, IV, and V dyslipidemia; however, a more favorable effect on the overall lipoprotein profile was observed **only** in the Type V patient population defined by the applicant as those patients having triglyceride (Tg) levels ≥ 750 mg/dL. For patients with Types IIb and IV dyslipidemia who also have elevations in LDL-C (as well as apo B and non-HDL-C) and are at risk for CV disease, Omacor® therapy was associated with an increase in LDL-C and other atherogenic lipid biomarkers including apo B and the LDL-C to HDL-C ratio. These increases may negate a potential cardioprotective effect of Tg-lowering observed in the Type IIb and IV patients.

A prospectively conducted clinical trial suggests a reduction in CV events in the secondary prevention population. However, this study used omega-3-fatty acids 1 gram daily which resulted in no increase in cholesterol levels. Conversely, a prospectively conducted clinical trial comparing Omacor 4 gram per day to placebo in patients with a recent MI showed no significant reduction in subsequent cardiac events despite significant reductions in Tg levels and significant increases in HDL-C levels. It is not known if cardioprotection is observed only at the lower dose of omega-3-fatty acids or if increasing the dose results in negative lipid effects that might offset the clinical benefits. Until more definitive evidence for CV risk reduction is available for Omacor®, this product should not be approved for Tg-lowering in the Type IIb and IV patient population who are at greater risk for CVD. Omacor® is effective in lowering Tg levels in Type V patients without evidence of unfavorably altering other lipoprotein parameters. Consequently, this product may have a clinical benefit in these patients who have more severely elevated Tg levels and are at risk for pancreatitis.

No serious safety concerns were noted in the review of Omacor 4 grams administered daily.

9.2 Recommendation on Regulatory Action

1. As an adjunct to diet to reduce TG levels in adult patients
- 2.

This reviewer recommends approval for the application in patients with elevated Tg levels in Type V dyslipidemia.

cardiovascular events. Clinical outcomes data from adequate and well-designed studies are not available for Omacor® to reassure prescribers that the increase in LDL-C is not a clinically significant finding.

9.3 Labeling Recommendations

The primary labeling recommendation for this submission is that the indication will be limited to the treatment of hypertriglyceridemia in Type V dyslipidemia. The Clinical Trials section under CLINICAL PHARMACOLOGY should summarize efficacy results from only those studies representative of the Type V population. Of the 8 Category 1 studies, two enrolled patients with severe hypertriglyceridemia whose baseline characteristics reflect the Type V patient population. Dr. Lee Pian of the Office of Biometrics presented pooled efficacy data for these two studies. The following table summarizes the baseline lipid profile for studies K85-94010 and K85-95009.

Table 35. Baseline Lipid Characteristics of Pooled Studies
in Severe Hypertriglyceridemics

	Placebo	K85	Total
Triglyceride	n=42	n=42	n=84
Mean (SD)	847.6 (274.2)	881 (341.9)	864.5 (308.5)
(Max, Min)	┌		┐
LDL	n=42	n=42	n=84

Mean (SD) (Max, Min)	116.4 (54.2) C	94.8 (42.4)	105.6 (49.6) J
HDL	n=42	n=42	n=84
Mean (SD) (Max, Min)	24.4 (8.2) C	24.2 (11.8)	24.3 (10.1) J
TC	n=42	n=42	n=84
Mean (SD) (Max, Min)	316.6 (76.4) C	299.7 (91.6)	308.1 (84.2) J

The following table summarizes the median percent changes for Tg and other lipid parameters for these two studies.

Table 36. Pooled Data for Severe Hypertriglyceridemia,
 Median % Change from Baseline

	Tg		LDL		CHOL		HDL		VLDL		NHDL	
	N	change	N	change	N	change	N	change	N	change	N	change
Placebo	42	6.7	42	-4.8	42	-1.7	42	0	41	-0.9	42	-3.6
K85 4 g	42	44.9	42	44.5	41	-9.7	41	9.1	41	41.7	41	13.8
Difference		51.6		49.3		-8		9.1		40.8		10.2

Labeling recommendations from other disciplines are made in their separate reviews.

9.4 Recommendation on Postmarketing Actions

9.3.1 Risk Management Activity

None. No safety signals were noted in the marketing application which would require specific post-marketing safety evaluation other than outlined under 21 CFR 314.80.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

14 pages redacted from this section of
the approval package consisted of draft labeling

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

/s/

Mary Parks

11/8/04 10:29:56 AM

MEDICAL OFFICER

This application has been split

has been submitted into DFS The same review

David Orloff

11/8/04 04:42:06 PM

MEDICAL OFFICER

Concur with Dr. Parks