CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-078

MEDICAL REVIEW(S)

CLINICAL REVIEW

Application Type	NDA
Submission Number	22-078
Letter Date	April 17, 2007
Stamp Date	April 17, 2007
PDUFA Goal Date	February 17, 2008
Reviewer Name	Iffat N. Chowdhury, MD
Review Completion Date	February 15, 2008
Established Name	Niaspan and simvastatin
(Proposed) Trade Name	Simcor®
Therapeutic Class	Lipid-altering agent
Applicant	Abbott
Priority Designation	S
Formulation	Oral tablet
Dosing Regimen	Once daily
Indication	Hypercholesterolemia
Intended Population	Patients with type IIa, IIb, and IV hyperlipidemia when treatment with simvastatin or niacin extended-release monotherapy is inadequate

Table of Contents

Table of Tables:

Table of Figures:

EXECUTIVE SUMMARY

1.1 Recommendation on Regulatory Action

It is recommended that Simcor be approved with the following indication: To reduce total-C, LDL-C, non-HDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

It is also recommended that Simcor be indicated to reduce TG in patients with hypertriglyceridemia (Fredrickson type IV hyperlipidemia) when treatment with simvastatin monotherapy or niacin extended-release monotherapy is considered inadequate.

1.2 Recommendation on Post marketing Actions

1.2.1 Risk Management Activity

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle, e.g., uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with simvastatin. There have also been reports of myopathy and/or rhabdomyolysis when simvastatin is used in combination with $\geq$ 1 gram/day of niacin. This reviewer is concerned with the potential increase in myopathy/rhabdomyolysis. The Applicant should be advised to closely monitor utilization of Simcor and myopathy/rhabdomyolysis following approval of this NDA.

Use of niacin extended-release (ER) and simvastatin have been associated with abnormal liver tests. Although there were no persistent increases to more than 3X the upper limit of normal in serum transaminases in the submitted clinical trials for this NDA, the Applicant should be advised to continue monitoring for liver abnormalities following approval of Simcor.

Use of niacin ER has also been associated with a rise in fasting blood sugar. The effect on fasting blood glucose with the use of Simcor is of concern. The open-label study submitted with this NDA also shows an increase in glycosylated hemoglobin in patients taking Simcor. The applicant should be advised to monitor for impaired glucose tolerance incidence post-approval.

1.2.2 Required Phase 4 Commitments

None

1.2.3 Other Phase 4 Requests

None

1.3 Summary of Clinical Findings

There were two completed Phase III clinical trials submitted to this NDA. SEACOAST compared the efficacy and safety of four different doses of Simcor with two different simvastatin doses. OCEANS was conducted to evaluate the incidence of flushing in two different Simcor titration regimens.

The data from the clinical safety and efficacy studies submitted to this NDA show Simcor's superiority compared with simvastatin monotherapy in reducing elevated non-high density lipoprotein (non-HDL-C), triglycerides (TG), Apolipoprotein B (Apo B), and Lipoprotein (a) [Lp(a)] and increasing high density lipoprotein (HDL-C) in patients with primary hypercholesterolemia (heterozygous familial and nonfamilial), and mixed dyslipidemia. Although Simcor reduces low density lipoprotein (LDL-C), the reductions are not statistically significant as compared to simvastatin monotherapy.

The primary objective for SEACOAST was to compare the effects of Simcor to simvastatin on non-HDL-C levels in patients who had LDL-C at goal, or had LDL-C which had not decreased with simvastatin monotherapy. The results support the use of Simcor as therapy for reducing elevated non-HDL-C. Specifically, Simcor 1000/20mg and 2000/20mg were superior to simvastatin 20mg in lowering non-HDL-C. Simcor 1000/40mg and 2000/40mg were non-inferior to simvastatin 80mg in reducing non-HDL-C. Thus, Simcor was superior to the low-dose simvastatin in reducing non-HDL-C, but non-inferior to the high-dose simvastatin.

The results of the study also support Simcor's ability to improve other lipid endpoints. In comparison to simvastatin 20mg monotherapy, Simcor 1000/20mg and 2000/20mg were superior in reducing TG, Apo B, Lp (a) and in raising HDL-C levels. Simcor 1000/40mg and 2000/40mg were also superior to the simvastatin 80mg in lowering TG, Apo B, Lp (a) and in raising HDL-C.

However, Simcor provided no greater advantage over simvastatin monotherapy in reducing LDL-C. Specifically, Simcor reduced LDL-C, but the reduction was not statistically significantly greater than that provided by simvastatin monotherapy. Moreover, there was a requisite titration period of approximately 12 weeks due to the tolerability issues associated with Niaspan use. Therefore, these data do not support

Although the SEACOAST study results were not reproduced in a second controlled trial (i.e., a second study was not required for NDA filing), there is sufficient clinical experience with the marketed products Niaspan and simvastatin to support a combination tablet of these two products.

The long-term, uncontrolled study OCEANS found that Simcor produced decreases in non-HDL-C, LDL-C and TG, and increases in HDL-C. These results were durable over the 52 weeks of the study.

The safety findings in both the controlled and uncontrolled clinical studies suggest that Simcor is relatively safe for chronic administration. The majority of adverse events were not serious, and resolved when Simcor was discontinued or the dose was decreased.

Simcor was poorly tolerated with discontinuations secondary to adverse events (flushing) in both the 6 month and longer-term studies. Women tended to be bothered more by flushing than men. Flushing events did not decrease over time in the controlled study suggesting that tolerance to flushing does not necessarily occur with chronic use of Simcor. In the open-label study in which patients were randomized into one of two different titration regimens, the incidence of flushing did not differ between the two titration regimens. (Appendix B)

1.3.1 Brief Overview of Clinical Program

Two Phase III clinical studies were submitted in support of this NDA. Three Phase I biopharmaceutical studies were also submitted and reviewed by Dr. Sang Chung of the Office of Clinical Pharmacology/Division of Clinical Pharmacology 2.

SEACOAST, the pivotal efficacy study, was a double-blind, active-controlled 24-week study in 641 patients. The study design reflected this Agency's requirement that the lipid-modifying effects of Simcor be assessed only in patients who failed to meet NCEP target (or options) for non-HDL-C after adequate treatment with simvastatin monotherapy (20 mg and/or 40 mg). Patients were randomized into either Dose Group A or B depending on their non-HDL-C and LDL-C levels as well as prior treatment history. Thus, Dose Group A randomized patients with elevated non-HDL-C with at-goal LDL-C and Dose Group B randomized patients with elevated non-HDL-C regardless of LDL-C goal status. Non-HDL-C and LDL-C criteria were based either on NCEP-III Treatment Options or Goals.

Randomization occurred 2:2:1 to simvastatin 20mg, Simcor 1000/20mg and Simcor 2000/20mg for Dose Group A and 3:3:2 to simvastatin 80mg, Simcor 1000/40mg and Simcor 2000/40mg for Dose Group B.

SEACOAST was designed to assess the efficacy and safety of Simcor in modifying lipid parameters relative to simvastatin alone. The primary efficacy endpoint was the percentage change from baseline in non-HDL-C among treatment groups. Secondary endpoints included changes from baseline in LDL-C, HDL-C, TC, TG, Lp (a), Apo B, and other parameters.

OCEANS was a 52-week, open-label, multi-center study in 509 patients, evaluating the safety and tolerability of treatment with two different titration regimens of Simcor in patients with primary type II hyperlipidemia and mixed dyslipidemia. The titration schedule is displayed below.

Table 1: Simcor Titration Schedule in OCEANS

NS Titration Schedule	Weeks 0–4	Week 5–8	Week 9–12	Weeks 13–52
A	500/40	1000/40	1500/40	2000/40
B	500/40	1000/40	2000/40	2000/40

Note: Doses expressed as mg niacin ER/mg simvastatin.

The secondary objective of OCEANS was to study the incremental effect of chronic combination therapy with Simcor 2000/40mg vs. a simvastatin 40mg treated baseline on lipid parameters.

1.3.2 Efficacy

In this NDA, the applicant has requested approval for Simcor, a combination product, for "use in patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia." The applicant has proposed Simcor

The efficacy data presented in this NDA show effective non-HDL-C and TG lowering as well as effective HDL-C raising; however, LDL-C lowering is ineffective as compared to simvastatin monotherapy.

Simcor can be recommended for patients in whom treatment with simvastatin monotherapy or extended-release niacin monotherapy is inadequate, according to the NCEP ATP III guidelines.

1.3.3 Safety

The safety findings in the two Phase III studies, SEACOAST and OCEANS, were similar. Overall, Simcor was not well tolerated, and more patients in the Simcor-exposed groups reported any AEs during study drug treatment compared with patients in the simvastatin group. This resulted in more Simcor-exposed patients discontinuing study drug treatment prior to study completion. Flushing was the most commonly reported reason for discontinuation in both

studies, and occurred more frequently in the Simcor-exposed groups. Female patients were somewhat more likely to be discontinued from the study than male patients, most commonly due to AEs, especially flushing.

The safety findings in both the controlled and uncontrolled clinical studies suggest that Simcor is relatively safe for chronic administration. The majority of AEs were not serious, and resolved when Simcor was discontinued or the dose was decreased. Furthermore, an extensive investigation for liver and muscle adverse effects in the AERS database did not show a strong safety signal for the co administered use of simvastatin with niacin extended-release.

Simcor was, however, poorly tolerated (approximately 25-30% drop-out rate in most of the studies). Tolerance to the side-effects of Simcor, particularly flushing, did not substantially improve with time during the 24-week trial. This will likely limit Simcor's clinical utility.

Simcor's side-effect profile was found to resemble that of Niaspan and other niacin products. As Niaspan and simvastatin are both widely prescribed, marketed products, there is considerable clinical experience with both of these drugs and their safety profiles are well established. As Simcor is a combination product, it is recommended that the Simcor label contain the same precautions, warnings, and contraindications as are contained in both the simvastatin and Niaspan labels.

1.3.4 Dosing Regimen and Administration

According to the Applicant, the Simcor doses selected for efficacy assessment (1000/20, 2000/20, 1000/40, and 2000/40) were those that were felt to offer meaningful clinical benefit for patients with dyslipidemia. However, the manufactured tablet strengths of 500/20, 750/20 and 1000/20 would allow for Simcor dosing at 500/20, 750/20, 1000/20, 1000/40, 1500/40 and 2000/40. The 2000/20mg studied dose will not be captured by the tablet strengths offered. In order to take the equivalent of 2000/20 mg, patients will have to take one Simcor 1000/20 mg tablet and a second 1000mg Niaspan tablet. In this reviewer's opinion, this negates the purpose of a combination product.

1.3.5 Drug-Drug Interactions

Simvastatin is a substrate of CYP3A4. Simvastatin is metabolized by CYP3A4, but has no CYP3A4 inhibitory activity; therefore it is not expected to affect the plasma concentrations of other drugs metabolized by CYP3A4. Of the known drug-drug interactions listed in the current simvastatin label, the following observations were made in the current submission.

- Two patient concomitantly received cyclosporine and Simcor in SEACOAST
- Three patients concomitantly received verapamil and Simcor in SEACOAST

1.3.6 Special Populations

The effect of Simcor on the Apo B-containing lipoproteins tended to be greater in women than men while the effects on HDL-C and TG were generally consistent between men and women in Dose Group A. In Dose Group B, the effect of Simcor on the key efficacy endpoints (percent change from baseline to Week 24 in non-HDL-C, LDL-C, HDL-C, Total-C, TG, and Lp[a]) was generally consistent between men and women.

The efficacy findings were consistent between age categories ($\geq$ 65 years and < 65 years) in both Dose Group A and Dose Group B. Geriatric patients appeared to have at least as great a response to the lipid-altering effects of Simcor as non-geriatric patients.

Simcor is contraindicated in women who are or may become pregnant and in lactating mothers. Simcor may cause fetal harm when administered to pregnant women.

At this time, as hypercholesterolemia as a risk factor for CHD is primarily a concern for adult patients, the Applicant requested and was granted a pediatric waiver. No pediatric studies were performed and the Division is not aware of any studies that are currently planned for pediatric patients.

2 INTRODUCTION AND BACKGROUND

In this NDA, the applicant has requested approval for Simcor (simvastatin and niacin extended--release tablets) indicated for "use in patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia."

Niacin and simvastatin have complementary mechanisms of action with differing relative impacts on atherogenic particles. Niacin has an effect on a broad range of lipid particles including reduction of TG, LDL, VLDL and Lp [a]; it also can increase HDL.

Niacin ER is presently available by prescription at doses of 500 mg, 750 mg, and 1000 mg extended-release tablets for use in individuals with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia.

Simvastatin is a HMG-CoA reductase inhibitor that has potent effects on LDL and is indicated for treatment of hypercholesterolemia and to reduce the risk of coronary heart disease mortality and cardiovascular events. It is presently approved at once daily doses of 5 mg, 10 mg, 20 mg, 40 mg, or 80 mg for use in individuals at increased risk of atherosclerotic –related clinical events as a function of cholesterol level, coronary heart disease, and other risk factors.

Of note, NDA 22-078 was pre-assigned to Kos Life Sciences, Inc. In December 2006, Kos Life Sciences, Inc. became a wholly owned subsidiary of Abbott Laboratories and thus the application was transferred to Abbott Laboratories on March 15, 2007.

2.1 Product Information

Simcor is a new fixed-dose combination of simvastatin and niacin extended-release (ER) tablets. It is a lipid-lowering agent which will be manufactured in 500mg/20mg, 750mg/20mg, and 1000mg/20mg tablets. The applicant proposes Simcor be indicated as an adjunct to diet to reduce elevated total-C, LDL-C, non-HDL-C, Apo B, TG and — in patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia. Simcor® should be taken as a single daily dose at bedtime with a low-fat snack.

The statin component of Simcor, simvastatin, produces its lipid-lowering effect in two ways. First, as a consequence of its reversible inhibition of HMG-CoA reductase activity, it effects modest reductions in intracellular pools of cholesterol. This results in an increase in the number of LDL-receptors on cell surfaces and enhanced receptor-mediated catabolism and clearance of circulating LDL. Second, simvastatin inhibits LDL production by inhibiting hepatic synthesis of VLDL, the LDL precursor. In both normal volunteers and patients with hypercholesterolemia, treatment with simvastatin has been shown to reduce total cholesterol, LDL-C and apolipoprotein B. Simvastatin has also been shown to reduce VLDL-C and triglycerides and produce increases in HDL-C and apolipoprotein A.

Simvastatin is indicated for the primary prevention of coronary events in hypercholesterolemic patients, as well as the secondary prevention of cardiovascular events in patients with clinically

evident coronary heart disease. It is indicated as well, as an adjunct to diet, to reduce elevated Total-C, LDL-C, Apo B, and TG levels and to increase HDL-C in patients with primary hypercholesterolemia and mixed dyslipidemia (Frederickson Type IIa and IIb); as an adjunct to diet for the treatment of patients with elevated serum triglyceride levels (Frederickson Type IV); and for the treatment of patients with primary dysbetalipoproteinemia (Fredrickson Type III) who do not respond adequately to diet.

The niacin component of Simcor, in the form of niacin-ER (Niaspan®), inhibits mobilization of free fatty acids from peripheral adipose tissue to the liver, consequently reducing hepatic synthesis of both VLDL and triglycerides. Although predominately due to lower triglyceride levels, the reduction in LDL is also due to reduced VLDL, and therefore less lipolysis to LDL. Niacin increases HDL by blocking hepatic uptake of apolipoprotein A-I, thereby decreasing HDL clearance and increasing amounts of HDL available for reverse cholesterol uptake. [1] As with statins, niacin promotes regression of atherosclerotic lesions, decreases coronary events, and reduces mortality in patients with CHD.

Niacin immediate-release formulations have been in clinical use for decades as a treatment to reduce elevated TC and TG levels, and for the treatment of types II, III, IV, and V hyperlipoproteinemia... Its clinical use has been limited however, as niacin immediate-release has been poorly tolerated primarily due to flushing. Sustained-release formulations of niacin were developed to try to reduce the incidence of side-effects and improve tolerability; however, early attempts at development of sustained-release preparations were unsuccessful secondary to severe liver toxicities (including fulminant liver necrosis) associated with these formulations. Niaspan® (niacin extended-release) was approved by the Agency in 1997, and has a safety profile similar to the immediate-release formulations.

2.2 Currently Available Treatment for Indications

The drugs used to treat dysplipidemias are of six classes: hydroxymethylglutaryl CoA (HMG CoA) reductase inhibitors (statins), fibric acid derivatives, nicotinic acid derivatives, cholesterol binding resins (bile acid sequestrants), cholesterol absorption inhibitors and fish oils. Simvastatin is a member of the statin class (HMG-CoA reductase inhibitors) used for the treatment of dyslipidemias; other statins include atorvastatin, fluvastatin, lovastatin, rosuvastatin, and pravastatin.

Niacin ER is a member of the nicotinic acid derivatives. It is a water soluble vitamin (vitamin B_3) with antilipemic action. The version of niacin used in Simcor is Niaspan® (Kos/Abbott Pharmaceuticals). Other niacin products available by prescription include Niacor (Upsher-

1 Worz, CR. et al. "Treating Dyslipidemic Patients with Lipid-Modifying and Combination Therapies." *Pharmacotherapy* 2003; 23[5]: 625-637.

Smith): 500 mg tablets; nicotinic acid (various manufacturers; eg, Rugby): 500 mg sustained-release capsules; 500 mg timed-release capsules.

Niacin is also available over-the-counter from various manufacturers in a range of 50 mg to 500 mg as immediate release, sustained release, and extended release forms. Various foods are also good sources of niacin such as liver, meat, fish, poultry, whole-grain and enriched breads and cereals, nuts, legumes, and green vegetables.

Niacinamide (nicotinamide) is the amide metabolite of niacin. Niacinamide is used to prevent and treat niacin deficiency and pellagra; it does not cause vasodilatation or flushing nor does it affect lipid levels. Niacinamide is available over-the-counter and by prescription.

2.3 Availability of Proposed Active Ingredient in the United States

Simvastatin and extended-release niacin are widely available by prescription in the United States. Originally marketed as Zocor®, simvastatin is currently available in generic form. The version of niacin used in Simcor is Niaspan® (Kos/Abbott Pharmaceuticals). Niaspan (niacin extended-release) was approved by the Agency in 1997.

2.4 Important Issues With Pharmacologically Related Products

A related pharmacologic product, Advicor® (lovastatin and Niaspan® fixed-dose combination) was approved on December 17, 2001, for the treatment of hypercholesterolemia. The initial Advicor® label stated Advicor® "is not indicated for initial therapy". Subsequently, the label was revised on April 6, 2007. The new label provided for the removal of second line therapy indication.

A study conducted by Alsheikh-Ali and colleagues examined the incidence of adverse events with Advicor® compared to monotherapy with lovastatin, pravastatin, atorvastatin, simvastatin or niacin.[2] Adverse events reported to the Food and Drug Administration from 1999 to March 2005 in which one of these drugs was reported suspect was reviewed. The rate of serious adverse events associated with the combination lovastatin/niacin-ER was similar to that of lovastatin or niacin-ER alone, and significantly less than that of atorvastatin or simvastatin. Likewise, the rates of liver adverse events and rhabdomyolysis associated with lovastatin/niacin-ER were similar to those of the other statins or niacin-ER alone and lower than those of simvastatin associated rhabdomyolysis reports ($p < 0.01$). Concomitant niacin-ER use in statin-associated adverse events was rare (<1%). The authors concluded the results should encourage the safe use of Advicor® in appropriate high-risk patients.

2 Alsheikh-Ali, A. et al. Safety of Lovastatin/Extended Release Niacin Compared with Lovastatin Alone, Atorvastatin Alone, Pravastatin Alone and Simvastatin Alone. *American Journal of Cardiology*.2007; 99:379-381.

The total number of patients who filled a prescription for Advicor® is shown below (table excerpted from review by Dr. Borders-Hemphill in the Office of Surveillance and Epidemiology). Note proprietary drug use databases licensed by the Agency were used in the analysis (Appendix D). From 2002-2006, the [redacted] strength was the most commonly dispensed strength of Advicor® annually, accounting for approximately [redacted] of all strengths, on average. During year 2006, over [redacted] patients filled an Advicor® prescription and over [redacted] patients filled prescriptions for the [redacted] strength.

Table 2: Projected Number of Patients Who Filled a Prescription for Advicor® from a U.S. Retail Pharmacy, 2002-2006

Total	Strength	2002	2003	2004	2005	2006
ADVICOR®	1000/40					
	1000/20					
	500/20					
	750/20					

Subtotals may not sum exactly due to rounding because of patients aging during the study period (the cohort effect); patients may be counted more than once in the individual age categories.
Duplicate PATs for 1000/20 and 500/20 are shown.
Do not add across years to get a cumulative total.
Verispan LLC, Vector One®: Total Patient Tracker (TPT) for calendar years 2002-2006.
Data extracted 9-24-07. Source file: 2007_1782_TPT_9-24-07 Advicor 2002-2006.

2.5 Presubmission Regulatory Activity

At the pre-IND stage, the applicant proposed a randomized controlled trial comparing niacin alone, simvastatin alone, and combination therapy, with various doses of each comparator.[3] In response, the Agency requested an add-on study instead, with the intent to reflect the possible use of Simcor as add-on therapy as per the NCEP ATP III guidelines. The Agency indicated that a study where patients start with simvastatin alone and then add on niacin would be adequate, and a second study starting with niacin and adding simvastatin would not be necessary.

The following table summarizes the presubmission regulatory activity between Kos/ Abbott and the Agency,

3 See meeting minutes provided by applicant to the pre-IND meeting (teleconference) held on November 12, 2002.

Table 3: Presubmission Regulatory Activity

DATE	REQUEST	OUTCOME
October 26, 2006	Pediatric waiver	Granted December 07, 2006
October 05, 2006	Waive requirement for domain data listing and patient profile listings	Yes, since in e-datasets. Reserve the right to request during review.
September 26, 2006 (Pre-NDA meeting)	Does FDA want legacy study reports as review aids confirming BE of niacin tablets manufactured	Yes.
	Fully electronic except forms requiring signature?	Yes. Forms with original signatures are in archival jacket.
	No toxicology studies need to be performed. Nonclinical will be based on literature and legacy studies.	Agreed.
	No food effect study.	Agreed.
	No QTC evaluation required.	Agreed.
	CRFs provided for deaths, SAEs, and drops due to AEs (except flush-only drops).	Agreed.
	Annotated CRFs for final current protocols.	Agreed.
	Statistical testing for SEACOAST step-down manner.	Agreed.
	Categorical exclusion from an environmental assessment	Calculations required.

	Niacin DMF supports this part of drug substance due to previous review in NDAs 20-381 & 21-249.	Yes, plus brief section on general properties, regulatory specifications, and mfr site information.
	Summary information for simvastatin active plus reference to DMF	Yes, include regulatory specifications and mfr. site information
	Proposed list of drug product reports ok?	Agreed. Comment on proposed product specification: as long as comparative niacin dissolution supports testing in-process material rather than finished product.
June 01, 2006	FDA requested an in-use stability study.	Performed.
	6 months of primary stability still acceptable for initial filing (with addition of BHA) and 12 months of data submitted during review?	Yes.
	Is a BE study needed to demonstrate no change in simvastatin availability based on addition of BHA?	Not needed if simvastatin dissolution data are similar
	Provide simvastatin dissolution data across tablet strengths.	Performed
February 23, 2006	Since NDA is an eCTD with one controlled study and others are open-label studies, are ISS and ISEs required?	No, as different methodologies applied.
January 31, 2006	Allow OCEANS study to end at 24 weeks instead of 52 weeks since exposure met.	Agreed
August 22, 2005 (Teleconference)	Exposure of 100 for one year and 450 for 6 months.	Agreed

March 14, 2005 (Teleconference)	non-HDL primary endpoint for both clinical studies?	Agreed
November 17, 2003	Is it acceptable to use 15% rather than 12% for LDL stability criteria during qualification of patients? Yes.	Yes
November 12, 2002 Teleconference	Basic study design	Agreed

2.6 Other Relevant Background Information

A consult was requested from the Office of Surveillance and Epidemiology (OSE) to conduct a concurrency analysis for simvastatin use with Niaspan®. The following is an excerpt from that review. Note proprietary drug use databases licensed by the Agency were used in the analysis (Appendix D). See review by Dr. Borders-Hemphill for complete report.

- Overall, approximately **1%** of unprojected patients who filled a prescription for simvastatin concurrently filled a prescription for Niaspan® per year of this review.
- For every year examined in this review, there were a greater absolute number of concurrent patients filling a prescription for simvastatin 40 mg with a prescription for Niaspan® 500 mg on the same day than for the other strengths of these drugs.
- However, the greatest **proportion** of simvastatin patients receiving Niaspan® concurrent therapy was with 80 mg of simvastatin and 500 mg of Niaspan®.
- Simvastatin 20 mg with Niaspan® 750 mg had the lowest percentage of concurrency for all years of this review.

The Office of Surveillance and Epidemiology also assessed *physicians' intentions* for concurrent product use for simvastatin/Zocor® and Niaspan®. From 2002-2006, concurrent product use between simvastatin/Zocor® and Niaspan® represented around 1% of all simvastatin/Zocor® occurrences and close to 13% of Niaspan® occurrences.

3 SIGNIFICANT FINDINGS FROM OTHER REVIEW DISCIPLINES

3.1 CMC (and Product Microbiology, if Applicable)

Please see Dr. John Hill's CMC review for complete details.

3.2 Animal Pharmacology/Toxicology

No new data were submitted.

4 DATA SOURCES, REVIEW STRATEGY, AND DATA INTEGRITY

4.1 Sources of Clinical Data

In this NDA, the applicant presents the results of one randomized active-controlled trial (SEACOAST), one completed open-label safety trial (OCEANS), and a four-month safety update on an ongoing open-label trial (SUPREME). This NDA may be found in the FDA electronic document room via the path \\CDSESUB1\EVSPROD\NDA022078\000.

A literature review was conducted (see Section 10.3 for references). Adverse event data in the FDA's Adverse Event Reporting System (AERS) database were also reviewed for evidence of hepatic and musculoskeletal adverse events with simvastatin and niacin ER.

4.2 Tables of Clinical Studies

Table 4: Clinical studies considered in current submission

STUDY	STUDY REGION	DESIGN	TREATMENT GROUPS	DURATION OF TREATMENT	NUMBER OF PATIENTS
SEACOAST	U.S., Argentina Columbia Chile Russia	Randomized, double-blind parallel-arm active-controlled	4 doses of Simcor vs. 2 doses of simvastatin monotherapy (6 arms)	24 weeks	641
OCEANS	71 sites in the U.S.	Randomized, open-label parallel-arm uncontrolled	2 titration schedules of Simcor 2000/40mg	52 weeks	509
SUPREME	U.S.	Randomized, open-label, parallel arm, active-controlled	Simcor 2000/40mg vs. atorvastatin 40mg	12 weeks	57

4.3 Review Strategy

This reviewer's general approach to the review is described in Section 4.1, Sources of Clinical Data. This review describes and analyzes the data supporting safety and efficacy of Simcor in hypercholesterolemic patients. This is a combined medical and statistical review.

4.4 Data Quality and Integrity

A review was conducted at two clinical sites by the Division of Scientific Investigation (DSI). These sites were chosen because greater than 25% of patients screened were enrolled (36% and 41%). There were minor deficiencies reported by DSI at both sites. However, the overall data appeared acceptable in support of this NDA. Please see the complete DSI report by Andrea Slavin.

SEACOAST, OCEANS and SUPREME were conducted by Abbott/KOS in compliance with Good Clinical Practice (GCP) requirements. As certified in the submission, no debarred investigators were used in the conduct of these studies.

4.5 Compliance with Good Clinical Practices

There was a site-specific issue with the Russian site RU02. Abbott/Kos Pharmaceuticals discovered that the site of Principal Investigator Professor Olga D. Ostroumova, Moscow City Hospital #23, Moscow, Russia (RU02) was inspected in February 2006 for a study conducted by another sponsor. This site received a FDA Form 483 followed by an FDA warning letter issued on August 18, 2006 for "failure to maintain adequate and accurate case histories that record all observations and data pertinent to the investigation". According to Abbott/Kos documents, site RU02 underwent an audit for SEACOAST conducted by a third party on January 15-19, 2007. The existence of all 20 subjects from that site was confirmed, however, visual inspection of subject laboratory data showed suspicious occurrences of similar data for patients who had clinic visits on the same day. A subinvestigator, Dr. [redacted] was dismissed from the site as the person responsible.

Abbott/Kos Pharmaceuticals performed an objective assessment of the apparent similarities of subject data by writing a computer program to analyze the data. The program identified 10 pairs which were made up by 12 patients. The list of subjects is found in the Appendix of the SEACOAST study. No suspicious lab pairs occurred after February 2006 and appear to coincide with the FDA inspection and removal of the subinvestigator.

Abbott/Kos Pharmaceuticals decided the *primary dataset for the efficacy* analyses would be that obtained *after removal* of all data from all 20 subjects from site RU02. The primary datasets for the safety analyses would include all subjects including RU02. It was also decided that the dataset defined by removing only the 10 suspect data pairs would also be analyzed for efficacy.

4.6 Financial Disclosures

Under the applicable regulations, the Applicant provided a list of clinical investigators who conducted clinical studies and certified and/or disclosed financial arrangements as follows:

SEACOAST:

- [redacted] MD (Site [redacted]) has received consulting and speaking fees that total approximately $32,051.
- [redacted] MD (Site [redacted]) has received consulting and speaking fees that total approximately $45,984.
- [redacted] MD (Site [redacted]) has received both grants to fund ongoing research and honoraria for speaking that total approximately $95,645.
- [redacted] MD (Site [redacted]) has received consulting and speaking fees that total approximately $26,555.

OCEANS:

- [redacted], MD (Site [redacted]) has received consulting and speaking fees that total approximately $41,782.
- [redacted] MD (Site [redacted]) has received consulting and speaking fees that total approximately $158,324.
- [redacted] MD (Site [redacted]) received both grants to fund ongoing research and honoraria for speaking that total approximately $34,431.
- [redacted] MD (Site [redacted]) has received consulting and speaking fees that total approximately $30,199.
- [redacted], MD (Site [redacted]) has received consulting and speaking fees that total approximately $46,796.

These financial relationships were unlikely to have influenced the study results. The Applicant has taken steps to minimize potential bias. Furthermore, the Applicant certified that no financial arrangements with an investigator have been made where study outcome could affect compensation.

5 CLINICAL PHARMACOLOGY

The Applicant submitted three Phase I biopharmaceutical studies with this NDA. The pivotal bioavailability (BA) study, 019-03-04-CP, will be briefly summarized in this clinical review. Please see the clinical pharmacology review by Dr. Sang Chung for a complete analysis of the Phase I biopharmaceutical studies.

5.1 Pharmacokinetics

The objective of study 019-03-04-CP was to compare the bioavailability of niacin and simvastatin from a combination tablet relative to administration of Niaspan® alone, Zocor® alone, and the co-administration of Niaspan® and Zocor®.

Forty-four healthy patients (21 men and 23 women) were enrolled in this randomized, open-label, single-dose, four-way crossover study, with four sequences and four periods, lasting approximately 6 days each with a minimum 10 days washout between each treatment. All patients received each of the following four treatments – one treatment during each of the four periods:

- NS (Simcor): 2000/40 mg niacin/simvastatin (2 tablets each containing 1000 mg niacin ER and 20 mg simvastatin)
- NSP (Niaspan®): 2000 mg niacin ER (2 x 1000 mg Niaspan® tablets)
- ZOC (Zocor®): 40 mg simvastatin (2 x 20 mg Zocor® tablets)
- NSP (Niaspan®) + ZOC (Zocor®): 2000 mg niacin ER (2 x 1000 mg Niaspan® tablets) and 40 mg simvastatin (2 x 20 mg Zocor® tablets) co administered.

PK Blood Samples were collected at the following times: Pre-dose (within 30 min of the dose of the study drug) and 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 6, 8, 10, 12, 14, 16, and 24 hrs after dosing (16 samples/treatment).

PK Urine Collections were obtained at: -24 to -18, -18 to -12, -12 to -6, -6 to 0 hrs (i.e., prior to dosing), and then, 0 to 6, 6 to 12, 12 to 18, 18 to 24, 24 to 48, 48 to 72, and 72 to 96 hrs after dosing (11 samples/treatment). Niacin, NUA, N-methylnicotinamide (MNA), and Nmethyl- 2-pyridone-5-carboxamide (2PY) were assayed in all urine samples by validated LC/MS/MS methods.

Niacin:

The primary variables designed to evaluate Niacin rate and extent of absorption were NUA C_{max} and total urinary recovery of niacin and its three major metabolites (NUA, MNA, and 2PY) respectively. The 90% CI for the natural-log transformed ratios of these primary BA variables were within the 80-125% range for all comparisons indicating comparable bioavailability between treatments. Mean T_{max} values for NUA was approximately 5 hours for all the 3 treatments.

Simvastatin

Simvastatin is a pro-drug and simvastatin acid is the active metabolite for efficacy. Therefore, the primary endpoints in the comparative BA assessment include both simvastatin and simvastatin acid pharmacokinetic parameters.

According to the clinical pharmacology reviewer, Simvastatin C_{max} and AUC after Simcor® were 17% and 23% higher than those after Zocor® alone. The higher simvastatin AUC (23%) after Simcor® seems to be from the formulation interaction (NS vs. NSP+ZOR; 12% increase) and the drug interaction (NSP+ZOC vs. ZOC; 9.5% increase).

The mean T_{max} for simvastatin was around 2 hrs and the mean $t_{1/2}$ around 4.25 hrs for all three treatments.

Simvastatin acid

According to the clinical pharmacology reviewer, simvastatin acid C_{max} and AUC after Simcor® were 25% and 41% higher than those after Zocor® alone. The higher simvastatin acid AUC (41%) after Simcor® seems to be from the formulation interaction (NS vs. NSP+ZOR; 19% increase) and the drug interaction (NSP+ZOC vs. ZOC; 18% increase).

The mean T_{max} for simvastatin acid occurred later with the Simcor treatment (6.56 hrs) as compared to ZOC (5.05 hrs) and NSP+ZOC (5.76 hrs). The mean $t_{1/2}$ for all three treatments was between 4 and 5 hrs.

Thus administering Niaspan® plus Zocor® resulted in a 9% increase in simvastatin and an 18% increase in simvastatin acid AUC while administering Simcor resulted in a 23% increase in simvastatin and 41% increase in simvastatin acid as compared to Zocor®. This suggests that the differences in bioavailability for simvastatin and simvastatin acid from Simcor versus Zocor® are probably a combination of a drug-drug interaction and formulation differences.

Furthermore, from a previous study of Zocor® 80mg, the C_{max} and AUC for simvastatin acid were 3.92 ng/mL and 34.65 ng.hr/ml. This is comparable to the exposure to simvastatin acid from 2000/40mg Simcor (C_{max} 3.29 ng/ml and AUC 30.8 ng hr/ml). Thus, the exposure of simvastatin and simvastatin acid after Simcor was lower than those of the possible lowest simvastatin and simvastatin acid after Zocor® 80mg. This reviewer concludes that the exposure increases of simvastatin and simvastatin acid after Simcor® administration vs. those of Zocor® are comparable to previous experience and is not clinically significant.

6 INTEGRATED REVIEW OF EFFICACY

6.1 Indication

The indication being sought by the applicant is "to reduce elevated Total-C, LDL-C, non-HDL-C, Apo B, TG, [redacted] and to increase HDL-C in patients with primary hypercholesterolemia [redacted] mixed dyslipidemia, and hypertriglyceridemia."

6.1.1 Methods

To support the efficacy of Simcor® in modifying lipid parameters, data from two Phase III studies (SEACOAST and OCEANS) were submitted. Pooling of the data from theses two studies was not possible because one study was controlled and the other was open-label. In terms of the efficacy analysis, only SEACOAST was considered to be relevant, as it was randomized, controlled, and double-blind.

6.1.2 General Discussion of Endpoints

The primary endpoint for SEACOAST was change from baseline to end of treatment in non-HDL-C. As combination therapy with simvastatin and Niaspan® has a major effect on the triglyceride-HDL-C axis, non-HDL-C was selected as the primary endpoint. In addition, for Dose Group A, entry criteria mandated at-goal LDL-C levels and elevated non-HDL-C levels; thus, the appropriate lipid endpoint was non-HDL-C.

Secondary efficacy endpoints were changes in LDL-C, HDL-C, TC, TG, and LP(a) from baseline to end of treatment. Other secondary variables were changes from baseline to end of treatment in apolipoprotein A-I, high-sensitivity C-reactive protein, lipoprotein A-1, TC to HDL-C ratio, LDL-C to HDL-C ratio and lipoprotein A-I to lipoprotein A-II ratio.

Efficacy was determined by comparing four doses of Simcor to two doses of simvastatin. In Dose Group A, Simcor 2000/20mg and 1000/20mg were compared to monotherapy with simvastatin 20mg. In Dose Group B, Simcor 2000/40mg and 1000/40mg were compared to monotherapy with simvastatin 80 mg.

The treatment arms in Dose Group A were designed for two superiority comparisons in a step-down manner. The first comparison was between Simcor 2000/20mg and simvastatin 20mg, and the second one between Simcor 1000/20mg and simvastatin 20mg. The second comparison would be conducted if the first comparison was statistically significant at a two-tailed α of 0.05. A statistically significant result supports the conclusion that the niacin component of the Simcor combination adds to the efficacy beyond what is observed with simvastatin monotherapy.

The treatment arms in Dose Group B were designed for a sequence of tests, using the step-down approach. The first test was a non-inferiority comparison of Simcor 2000/40mg compared to simvastatin 80mg. If non-inferiority was not ruled out at a test level of 0.05, then two more tests would be conducted: a) a non-inferiority comparison of Simcor 1000/40mg compared to simvastatin 80mg; and b) a superiority evaluation of Simcor 2000/40mg compared to simvastatin 80mg.

A pre-defined margin of difference for the primary endpoint, non-HDL-C, was determined at 6% for the non-inferiority approach to Dose Group B. The choice of 6% as a non-inferiority margin is based in part on the observation from clinical studies that doubling a statin dose generally results in a further decrease in LDL of approximately 6%. While most statin drugs have been approved on the basis of placebo-controlled studies, non-inferiority margins from 3% to 6% have been used in active-controlled studies.

6.1.3 Study Design

This was a 24-week, double-blind, active-controlled study of 641 patients randomized into either Dose Group A or Dose Group B depending on their non-HDL-C and LDL-C levels as well as prior treatment history. The study design reflected the Agency's requirement that the lipid-modifying effects of Simcor therapy be assessed only in patients who failed to meet NCEP target (or options) for non-HDL-C after adequate treatment with simvastatin monotherapy (20 mg and/or 40 mg). Thus, Dosing Group A randomized patients with elevated non-HDL-C with at- goal LDL-C and Dosing Group B randomized patients with elevated non-HDL-C regardless of LDL-C goal status. Non-HDL-C and LDL-C criteria were based either on NCEP-III Treatment Options or Goals.

The original study design included both a simvastatin 20mg and simvastatin 40mg treatment arm in Dose Group A. Per Amendment 3, the simvastatin 40mg arm was eliminated from Dose Group A as no efficacy comparisons were to be made relative to the treatment group (refer to the amendment in Section 10.1 Review of Individual Studies). Before the simvastatin 40mg arm was eliminated with Amendment 3, however, 5 patients had been randomized to this treatment arm.

In order to maintain double-study blind, 50mg immediate-release niacin was administered to patients in the simvastatin monotherapy treatment arms (both simvastatin 20mg and simvastatin 80mg). This dose of niacin has been shown in the literature not to affect lipid parameters.

6.1.4 Efficacy Findings

The SEACOAST study population had approximately 67% of patients with CHD or CHD risk equivalent. Overall, 21% of patients in Dose Group A and 36% in Dose Group B were diabetic. Patients who were 65 years of age or older represented about 23% of patients in Dose Group A and 36% of patients in Dose Group B.

Dose Group A had higher median non-HDL-C and LDL-C levels, moderately elevated median TG levels, and lower median HDL-C levels than Dose Group B at baseline. Profiles were consistent with a predominantly mixed dyslipidemic study population in Dose Group A. Dose Group B was characterized by type IIa hyperlipidemia.

Changes in lipid parameters are shown in Table 4. In Dose Group A, Simcor demonstrated dose-related reductions in non-HDL-C significantly greater than for simvastatin 20 mg monotherapy. In Dose Group B, Simcor was non-inferior to simvastatin 80 mg monotherapy in non-HDL-C reductions.

For LDL-C reductions, Simcor showed no greater advantage over simvastatin monotherapy. In Dose Group A, Simcor lowered LDL-C to the same extent as simvastatin 20mg. In Dose Group B, Simcor did not meet non-inferiority thresholds; simvastatin 80mg resulted in a greater reduction in LDL-C than Simcor.

All four doses of Simcor (1000/20mg, 2000/20mg, 1000/40mg, 2000/40mg) showed significantly greater reductions in TG, Apo B, and Lp(a) compared with simvastatin monotherapy. All doses of Simcor showed significantly greater elevations of HDL-C than simvastatin monotherapy.

Table 5: Changes in Lipid Parameters

	Dose Group A		Dose Group B	
Parameter	**Treatment Arm**	**Median % change from baseline to Wk 24 (p-value for Simcor vs. S20)**	**Treatment Arm**	**Median % change from baseline to Wk 24 (p-value for Simcor vs. S80)**
Non-HDL-C (mg/dL)	S20	-7.4	S80	-10.1
	NS 1000/20	-13.9 (p=0.007)	NS 1000/40	-11.3 (NI met)
	NS 2000/20	-22.5 (p<0.001)	NS 2000/40	-17.1 (NI met)
LDL-C (mg/dL)	S20	-7.1	S80	-12.7
	NS 1000/20	-13.1 (p=0.086)	NS 1000/40	-8.6 (NI not met)
	NS 2000/20	-14.2 (p=0.063)	NS 2000/40	-11.6 (NI not met)
HDL-C (mg/dL)	S20	6.7	S80	-1.0
	NS 1000/20	18.3 (p<0.001)	NS 1000/40	14.8 (p<0.001)
	NS 2000/20	24.9 (p<0.001)	NS 2000/40	21.9 (p<0.001)
TG (mg/dL)	S20	-15.3	S80	0.3
	NS 1000/20	-26.5 (p=0.001)	NS 1000/40	-22.8 (p<0.001)
	NS 2000/20	-38.0 (p<0.001)	NS 2000/40	-31.8 (p<0.001)
Total-C	S20	-4.1	S80	-7.0
	NS 1000/20	-7.2	NS 1000/40	-3.2
	NS 2000/20	-8.6 (p<0.05)	NS 2000/40	-6.5 (p<0.05)
Lp(a) (mg/dL)	S20	-7.6	S80	0.0
	NS 1000/20	-16.7 (p=0.042)	NS 1000/40	-16.7 (p=0.006)

	NS 2000/20	-25.0 (p<0.001)	NS 2000/40	-21.0 (p<0.001)
Apo B (mg/dL)	S20	-4.0	S80	-8.8
	NS 1000/20	-13.8 (p=0.004)	NS 1000/40	-10.1 (p=0.720)
	NS 2000/20	-18.1 (p<0.001)	NS 2000/40	-14.1 (p=0.198)
Total-C:HDL-C ratio	S20	-10.3	S80	-5.1
	NS 1000/20	-21.0 (p<0.001)	NS 1000/40	-16.2 (p<0.001)
	NS 2000/20	-31.3 (p<0.001)	NS 2000/40	-24.5 (p<0.001)
LDL-C:HDL-C ratio	S20	-13.4	S80	-12.6
	NS 1000/20	-26.3 (p<0.001)	NS 1000/40	-23.6 (p=0.003)
	NS 2000/20	-35.7 (p<0.001)	NS 2000/40	-28.7 (p<0.001)

NI = noninferiority margin

6.1.5 Efficacy Conclusions

The primary efficacy results support Simcor's advantage over simvastatin monotherapy for lowering of non-HDL levels. Specifically, Simcor 1000/20mg and 2000/20mg were superior to simvastatin 20mg in lowering non-HDL-C. In comparison to simvastatin 80mg, Simcor 1000/40 and 2000/40mg were non-inferior in reducing non-HDL-C.

The SEACOAST review showed that the LDL-C lowering observed with Simcor provided no greater advantage over simvastatin monotherapy. Specifically, simvastatin 20 mg monotherapy was comparable to Simcor 1000/20mg and 2000/20mg in lowering LDL-C. Non-inferiority was not met by the higher doses of Simcor (1000/40 and 2000/40mg) in comparison to simvastatin 80mg in lowering LDL-C. Moreover, there was a requisite titration period of approximately 12 weeks due to the tolerability issues associated with Niaspan use. Therefore, these data do not support the

Simcor was more effective on the TG-HDL axis and provided favorable effects on TG, Apo-B and Lp(a) compared with simvastatin monotherapy.

7 INTEGRATED REVIEW OF SAFETY

7.1 Methods and Findings

The safety information in this NDA was based on two Phase 3 trials: SEACOAST, a randomized controlled study and OCEANS, an open-label study. The applicant also submitted safety data from an on-going open-label study (SUPREME) as the 4-month Safety Update.

Due to differences in the Phase 3 study designs, the applicant did not include an Integrated Summary of Safety (ISS). Consequently, this review of safety focused primarily on the controlled data from the SEACOAST study. Safety information from the OCEANS and SUPREME trial, are reviewed in Appendix 10 (review of individual study reports).

The Safety population in SEACOAST consisted of 641 patients who received a study drug. There were 238 patients who received any dose of simvastatin monotherapy and 403 patients who received any dose of Simcor in six different treatment arms.

Safety endpoints included adverse events and laboratory parameters. The applicant defined a Treatment Emergent Adverse Event as any Adverse Event (AE) whose onset occurred after the initiation of study medication or increased in intensity or frequency after study medication was started and was at least remotely related to study medication. This reviewer included all reported AEs regardless of principle investigator attribution, as this was felt to be a more objective evaluation of the data. Adverse events in the data set included those occurring in randomized patients who took at least one dose of study medication.

Of note, the Applicant did not define flushing as an adverse event unless it met the criteria of serious AE or resulted in discontinuation from the study. Flushing episodes were documented in self-reported "flushing logs" which were different from adverse events recordings. Separation of flushing from the other adverse events resulted in a decrease in the number of total adverse events.

For example, the Applicant originally submitted there were 343 adverse event in the combined simvastatin treatment arms (N=238) and 631 adverse events in the combined Simcor treatment arms (N=403), for a total of 974 adverse events. After a request by this reviewer to combine all the adverse events including flushing, the adverse events increased to 1,753 adverse events in 238 patients who received any simvastatin monotherapy and 4,757 adverse events in 403 patients who received any Simcor treatment. Note that even patients in the simvastatin monotherapy arms received 50mg immediate-release niacin to maintain study blind.

7.1.1 Deaths

No deaths were reported in the SEACOAST study.

7.1.2 Other Serious Adverse Events

Eleven (2.7 %) patients on Simcor experienced a serious adverse event (SAE) during the treatment phase versus 6 patients (2.5%) on simvastatin for a total of 17 SAE.
The SAEs are presented below by treatment group in Table 6.

Table 6: Serious Adverse Events by Treatment Groups and Preferred Term

Serious adverse events by treatment group (all subjects)		
TREATMENT GROUP	**AGE/GENDER/RACE**	**PREFERRED TERM**
Simvastatin Overall (N=238)		
S20	57/M/Hispanic	Coronary artery atherosclerosis
S20	66/F/Hispanic	Syncope
S20	75/F/Caucasian	Atrial fibrillation;coronary artery disease aggravated Myocardial infarction
S40	74/F/Caucasian	Anaemia NOS;anaphylactic shock; Atrial fibrillation; CHF; sick sinus syndrome
S80	57/M/Caucasian	Cholecystitis NOS
S80	55/M/Caucasian	Depression; Hallucination Intervertebral disc herniation; Tremor
NS Overall (N=403)		
NS 1000/20	72/F/Asian	Fall
NS 1000/20	48/M/Caucasian	Transient ischemic attack
NS 1000/40	74/F/Black	Small intestinal Obstruction NOS
NS 1000/40	46/M/Black	Hypertension (pre-randomization)
NS 1000/40	56/M/Caucasian	Cholecystitis NOS; convulsions;pyrexia; respiatory failure; sepsis
NS 1000/40	40/M/Caucasian	Optic ischemic neuropathy
NS 1000/40	53/F/Hispanic	Diabetic Ulcer
NS 1000/40	43/M/Caucasian	Myocardial ischemia
NS 2000/20	68/M/Hispanic	Cerebral ischemia
NS 2000/20	34/F/Hispanic	Abortion spontaneous NOS
NS 2000/40	69/F/Caucasian	Appendicitis (pre-randomization)
NS 2000/40	69/F/Caucasian	Colitis ischemic; coronary artery disease aggravated
NS 2000/40	58/M/Hispanic	Coronary artery disease NOS

*NS=Simcor

Of note, this reviewer found a discrepancy in the number of SAEs between the SEACOAST dataset (19 patients) and the number contained in the Clinical Study Report (17 patients). Subsequently, the applicant submitted information that the two events in question occurred prior to randomization in two subjects. The event of appendicitis for subject CA03- 02458 started on February 28, 2005, and ended on March 2, 2005. This subject was randomized on March 9,

2005. The event of hypertension for subject NY04- 02251 started on February 26, 2005, and ended on February 26, 2005. This subject was randomized on April 22, 2005. The table above presents all SAEs and includes the two noted events.

7.1.3 Dropouts and Other Significant Adverse Events

Table 7: Study Completions/Discontinuations by Treatment Arms in Dose Group A*

	Simvastatin 20mg	Simcor 1000/20mg	Simcor 2000/20mg	Combined Simcor Group A
Randomized pts, who received study drug, N	114	123	64	187
Completed, N (%)	97 (85%)	85 (69%)	46 (72%)	131 (70%)
Discontinued, N (%)	17 (15%)	38 (31%)	18 (28%)	56 (30%)

* Source Table 1.5 Disposition of Subjects Dose Group A-Safety "T01-05.lst"from email submission by the Applicant on 1/31/2008

Table 8: Study Completions/Discontinuations by Treatment Arms in Dose Group B*

	Simvastatin 80mg	Simcor 1000/40mg	Simcor 2000/40mg	Combined Simcor Group B
Randomized pts who received study drug, N	119	116	100	216
Completed, N (%)	96 (81%)	89 (77%)	80 (80%)	169 (78 %)
Discontinued, N (%)	23 (19%)	27 (23%)	20 (20%)	47 (22%)

* Source Table 1.6 Disposition of Subjects Dose Group B-Safety "T01-06.lst"from email submission by the Applicant on 1/31/2008

There were more discontinuations from Simcor treatment arms than the simvastatin 20mg arm in Dose Group A. For example, 30% of patients who received any Simcor discontinued the study as compared to 15% who received simvastatin monotherapy.

However, patients in Dose Group B had different discontinuation patterns than those in Dose Group A. For example, 22% of patients who received Simcor dropped out as compared to 19% in the simvastatin 80mg monotherapy.

7.1.3.1 Overall profile of dropouts

The reasons for discontinuations from the study were mostly due to adverse events, followed by withdrawal of consent, protocol violations, and lost to follow-up. The following table is from the applicant's data.

Table 9: Reasons for Discontinuations – Dose Group A*

	Simvastatin 20mg	Simcor 1000/20mg	Simcor 2000/20mg	Combined Simcor Group A
	N=121	N=127	N=66	N=193
Total Discontinuations	17 (14.9%)	38 (30.9%)	18 (28.1%)	56 (29.9%)
Adverse Events	6 (5.3%)	16 (13.0%)	10 (15.6%)	26 (13.9%)
Protocol Violation	4 (3.5%)	3 (2.4%)	3 (4.7%)	6 (3.2%)
Withdrawal of Consent	5 (4.4%)	15 (12.2%)	4 (6.3%)	19 (10.2%)
Lost to Follow-up	1 (0.9%)	4 (3.3%)	0	4 (2.1%)
Other	1 (0.9%)	0	1 (1.6%)	1 (0.5%)

*Source: Table 9 SEACOST CSR

Table 10: Reasons for Discontinuations – Dose Group B*

	Simvastatin 80mg	Simcor 1000/40mg	Simcor 2000/40mg	Combined Simcor Group B
	N=123	N=118	N=102	N=220
Total Discontinuations	23 (19.3%)	27 (23.3%)	20 (20.0%)	47 (21.8%)
Adverse Events	8 (6.7%)	17 (14.7%)	13 (13.0%)	30 (13.9%)
Protocol Violation	2 (1.7%)	1 (0.9%)	1 (1.0%)	2 (.9%)
Withdrawal of Consent	8 (6.7%)	6 (5.2%)	5 (5.0%)	11 (5.1%)
Lost to Follow-up	0	0	0	0
Other	5 (4.2%)	3 (2.6%)	1 (1.0%)	4 (1.9%)

*Source: Table 9 SEACOAST CSR

Approximately 14% of patients who received Simcor discontinued the study because of an adverse event as compared to about 6% of patients on simvastatin monotherapy who discontinued due to an adverse event. Withdrawal of consent was the second leading reason for discontinuing the study after adverse events. In Dose Group A, 10.2% of patients on Simcor withdrew consent compared to 4.4% of simvastatin 20mg treatment arm. In Dose Group B, withdrawal of consent was similar in all 3 treatment arms (around 5.5%).

7.1.3.2 Adverse events associated with dropouts

Table 11 shows the most commonly reported AEs resulting in drug discontinuations.

The adverse event most often leading to study discontinuation was flushing. Six percent of patients receiving any Simcor discontinued due to flushing compared to 0.8% of patients on simvastatin monotherapy in whom flushing resulted in discontinuation from the study. Note that patients on simvastatin monotherapy received niacin to maintain the study blind.

Table 11: All Treatment-Emergent Adverse Events Leading to Discontinuation for >1 Simcor Patient, by Descending Frequency of Preferred Term *

	Combined Simvastatin[b]	Combined Simcor Group A	Combined Simcor Group B	Simcor Overall (Groups A & B)
Preferred Term[a]	**N=238**	**N=187**	**N=216**	**N=403**
Total patients with AEs leading to discontinuation	**16 (6.7)**	**27 (14.4)**	**28 (13.0)**	**55 (13.6)**
Flushing [c]	2 (0.8)	14 (7.5)	10 (4.6)	24 (6.0)
Abdominal pain NOS	2 (0.8)	2 (1.1)	2 (0.9)	4 (1.0)
Hypersensitivity NOS	0 (0.0)	1 (0.5)	2 (0.9)	3 (0.7)
Headache	0 (0.0)	3 (1.6)	0 (0.0)	3 (0.7)
Pruritus	0 (0.0)	0 (0.0)	2 (0.9)	2 (0.5)

a Descending frequency of preferred term is based on Simcor Overall column for all AEs. Subjects with >1 AE in a designated cell are counted once.
b Simvastatin Overall includes subjects from the S20, S40 and S80 arms.
c Flushing was to be recorded as an AE if considered an SAE or resulted in discontinuation from the study.
*Source Table 31 SEACOAST CSR

7.1.3.3 Other significant adverse events

Flushing events were recorded in patient (self)-administered logs, unlike other adverse events which were solicited during the office visit. This reviewer requested the addition of the self-

reported flushing data with other adverse events to further examine the total adverse events experienced by the patient. It is important to understand flushing events as an adverse event because adverse events contribute to medication compliance. Compliance rates are especially important for drugs used to treat chronic conditions.

For example, the Applicant submitted data in Table 26 of the SEACOAST clinical study report (CSR) that 27 (6.7%) of all treatment-emergent AEs in the combined Simcor treatment arms (N=403) were as a result of flushing. When this clinical reviewer asked the Applicant to include all reports of flushing, not just those resulting in discontinuation or reported as a SAE, that number increased to 235 (58.3%). In this reviewer's opinion, the 58.3% more accurately represents the number of flushing adverse events in patients taking Simcor. Thus, this reviewer recommends informing physicians in the label that up to 58% of patients taking any dose of Simcor had flushing.

Niacin, and therefore Simcor in this submission, is typically associated with a few common adverse events as documented in the literature. Review of a few of those selected adverse events in the treatment arms is shown below in Tables 12 and 13.

Table 12: SEACOAST Selected AEs Dose Group A*

Dose Group A		Simvastatin 20mg N=114	Simcor 1000/20mg N=123	Simcor 2000/20mg N=64	Simcor Group A Overall N=187
Body System	**MedDRA Term**	n (%)	n (%)	n (%)	n (%)
Vascular	Flushing	49 (43%)	64 (52%)	39 (60.9%)	103 (55.1%)
Gastrointestinal	Nausea	3 (2.6%)	4 (3.3%)	2 (3.1%)	6 (3.2%)
Skin and	Pruritus	0	2 (1.6%)	0	2 (1.1%)
subcutaneous tissue	Rash	1 (0.9%)	1 (0.8%)	0	1 (0.5%)

* Source: Table 5.2.1, Submission 0004 of NDA

Table 13: SEACOAST Selected AEs Dose Group B*

Dose Group B		Simvastatin 80 mg N=119	Simcor 1000/40mg N=116	Simcor 2000/40mg N=100	Simcor Group B Overall N=216
Body System	**MedDRA Term**	n (%)	n (%)	n (%)	n (%)
Vascular	Flushing	60 (50.4%)	65 (56%)	67 (67%)	132 (61.1%)

Gastrointestinal	Nausea	7 (5.9%)	3 (2.6%)	4 (4.0%)	7 (3.2%)
Skin and	Pruritus	0	5 (4.3%)	6 (6.0%)	11 (5.1%)
subcutaneous tissue	Rash	4 (3.4%)	2 (1.7%)	4 (4.0%)	6 (2.8%)

*Source: Table 5.2.2 Submission 0004 of NDA

Because the study design was such that even patients on simvastatin monotherapy received 50mg immediate-release niacin, the data for flushing is difficult to interpret. In Dose Group A, 55% of patients receiving Simcor flushed as compared to 43% of simvastatin 20mg. In Dose Group B, 61% of patients on Simcor reported flushing vs. 50% of patients on simvastatin 80mg.

Flushing events did not decrease from the beginning of the study to the end of the study indicating a lack of tolerance. Table 14 (below) from the applicant's original NDA shows the number of patient who flushed by week,

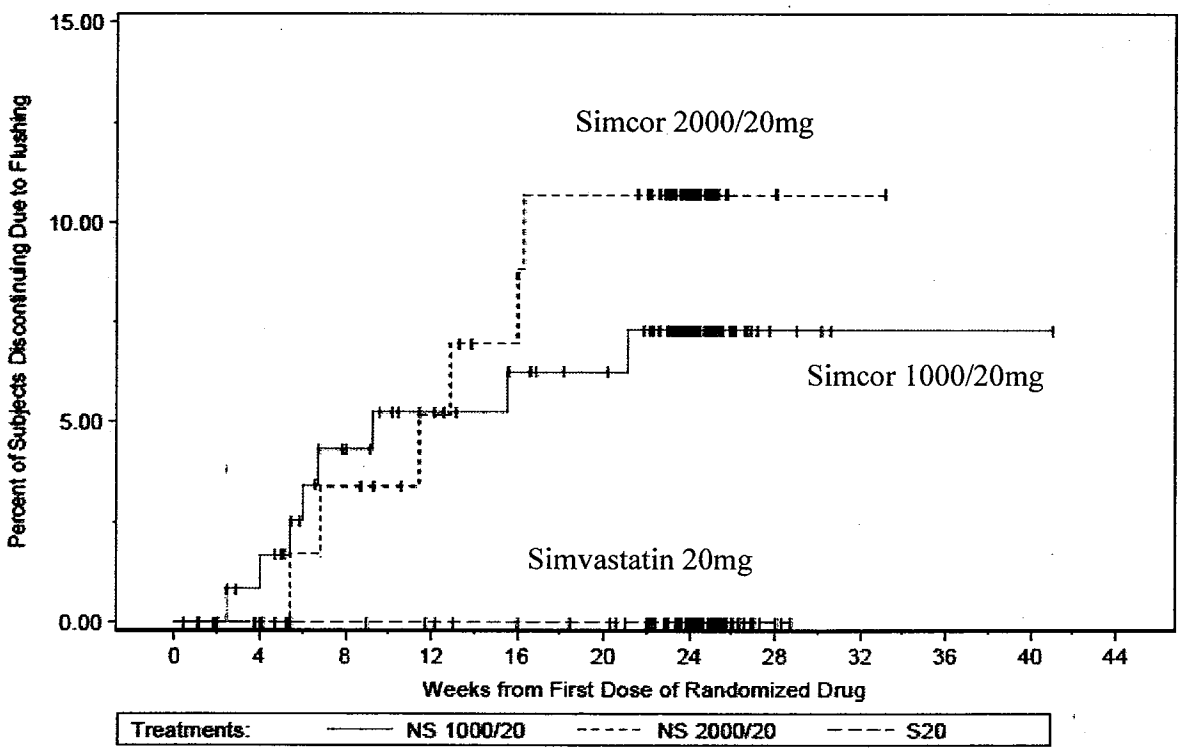
Table 14: Number (%) of Patients who Flushed by Week in Self –Report Logs*

	Simvastatin Overall		**Simcor Group A Overall**		**Simcor Group B Overall**		**Simcor Overall**	
Period	**M**	**n (%)**	**M**	**n (%)**	**M**	**n (%)**	**M**	**n (%)**
Week 1-4	230	76 (33.0)	178	50 (28.1)	210	81 (38.6)	388	131 (33.8)
Week 5-8	220	47 (21.4)	171	51 (29.8)	197	66 (33.5)	368	117 (31.8)
Week 9-12	216	39 (18.1)	164	48 (29.3)	194	54 (27.8)	358	102 (28.5)
Week 13-24	190	38 (20.0)	134	61 (45.5)	167	61 (36.5)	301	122 (40.5)
Overall	231	109 (47.2)	179	101 (56.4)	214	132 (61.7)	393	233 (59.3)

M=number of patients who completed aspirin/flushing logs; n=number of patients who flushed; %= n/M x 100.
Simvastatin Overall includes all patients from S20, S40 and S80 arms.
* Source: Table 28 SEACOAST CSR

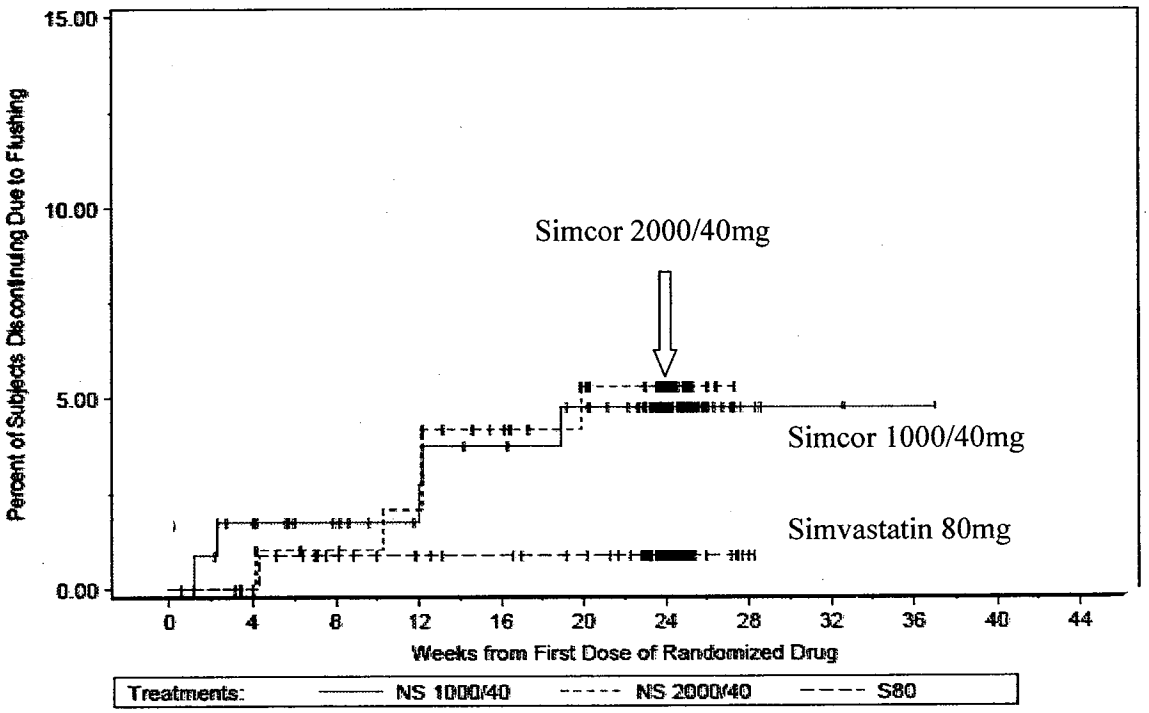
Although it is commonly accepted that patients develop tolerance to flushing, the study submitted conflicted with this clinical knowledge. For example, the percentage of patients who flushed in week 13-24 was higher (40.5%) than the percent of patients who flushed in week 1-4 (33.8%) in the Simcor overall group. Unabated flushing for a chronically administered medication can decrease patient compliance. The following Kaplan-Meier curves show the percentage of patient discontinuations due to flushing. The data is from the Applicant's CSR for SEACOAST.

Figure 1: Kaplan-Meier Curve Time to Discontinuation Due to Flushing Dose Group A



The higher dose of the niacin ER component may have contributed to the greater percentage of patients discontinuing from the Simcor 2000/20mg than Simcor 1000/20mg. Discontinuations occurred throughout the 24 week study for both Simcor treatment arms. The number of patients discontinuing from Simvastatin 20mg lower than for Simcor.

Figure 2: Kaplan-Meier Curve Time to Discontinuation Due to Flushing Dose Group B



In contrast to Group A, Simcor 2000/40mg discontinuation rate closely approximated the percentage of patients discontinuing due to flushing with Simcor 1000/40mg. Simvastatin 80mg monotherapy treatment arm had a higher percentage of discontinuations due to flushing compared with simvastatin 20mg. (Both simvastatin monotherapy arms received immediate-release 50mg niacin.)

7.1.4 Other Search Strategies

Numerous articles have been published in the last several years regarding the safety of combination therapy of lipid-lowering agents. This reviewer performed a literature search on the safety profile of statin and niacin combination therapy.

In the COMPELL study, 292 patients were randomized to four parallel arms: atorvastatin/niacin ER, rosuvastatin/niacin ER, simvastatin/ezetimibe, or rosuvastatin alone for 12 weeks. About 90% of those receiving simvastatin/ezetimibe or rosuvastatin completed the trial, compared with around 75–80% of those randomized to a statin/niacin ER. The difference is almost entirely accounted for by flushing or other cutaneous reactions. Table 15 shows the study drug dosing regimen for the COMPELL study.

Table 15: Study Drug Dosing Regimen-COMPELL[4]

Week	Treatment			
	Atorvastatin/ niacin ER	Rosuvastatin/ niacin ER	Simvastatin/ ezetimibe	Rosuvastatin
1–4	20 mg/500 mg	10 mg/500 mg	20 mg/10 mg	10 mg
5–8	20 mg/1000 mg	10 mg/1000 mg	20 mg/10 mg	20 mg
9–12	40 mg/2000 mg	20 mg/1000 mg	40 mg/10 mg	40 mg

In COMPELL, all groups had small increases within the normal range in liver transaminases and creatine kinase. No drug-related myopathy was observed, and no patient had elevated creatine kinase >5 times upper limit of normal. Very small relative increases in fasting glucose (+3 to +5 mg/dL) were observed with statin/niacin ER, although there were no significant changes in HbA1C levels. [4]

In another open-label study, IMPACT, the safety and compliance of 40 mg lovastatin /1000 mg niacin ER (Advicor) were examined in 4,499 patients with dyslipidemia. Patients were treated with 1 tablet (500 mg of niacin extended-release/20 mg of lovastatin) once nightly for 4 weeks and then 2 tablets for 8 weeks. Primary endpoints were study compliance, increases in liver transaminases to >3 times the upper limit of normal, and clinical myopathy. Compliance was 77%, with 3,245 patients completing the study. Flushing was the most common adverse event, reported by 18% of patients and leading to discontinuation by 6%. Incidence of increased aspartate aminotransferase and/or alanine aminotransferase >3 times the upper limit of normal was <0.3%. An increase of creatine phosphokinase to >5 times the upper limit of normal occurred in 0.2% of patients. No cases of drug-induced myopathy were observed.[5]

The HATS study (High-density cholesterol Atherosclerosis Treatment Study) randomized 160 subjects to placebo or simvastatin plus niacin (mean dose of simvastatin 13 mg and niacin 2.4 g) for three years. . Simvastatin plus niacin caused small but consistent increases in the levels of aspartate aminotransferase, creatine kinase, uric acid, and insulin, but not glucose. (see table below) [6]

4 McKenney, JM et al. Comparative effects on lipid levels of combination therapy with a statin and extended-release niacin or ezetimibe versus a statin alone (the COMPELL study). *Atherosclerosis.* 2007;192: 432-437.
5 Rubenfire, M. et el. Safety and Compliance with Once-Daily Niacin Extended-Release/ Lovastatin as Initial Therapy in the Impact of Medical Subspecialty on Patient Complicance to Treatment (IMPACT) Study. *American Journal of Cardiology.* 2004; 94: 306-311.
6 Brown, BG et al. Simvastatin and Niacin, Antioxidant Vitamins, or the Combination for the Prevention of Coronary Disease. *New England Journal of Medicine.* 2001; 345: 1583-92.

Table 16: Laboratory Results from HATS study

	Placebo (N=34)		SV + Niacin (N=33)	
Labs	At baseline	During therapy	At baseline	During therapy
AST (U/L)	22	24	23	29
CK (U/L)	76	86	78	96
Uric Acid (mg/dL)	6.2	6.2	5.8	6.3
Glucose (mg/dL)	98	99	102	105
Insulin (µU/mL)	24	26	26	31

In another study, Alsheikh-Ali and colleagues compared the prevalence of concomitant use of niacin ER in adverse event reports received by the United States Food and Drug Administration (1999 to March 2005) associated with statins[7] (See table below).

Table 17: Prevalence of concomitant use of extended-release (ER) niacin in adverse event reports (AERs) associated with commonly used statins[8]

	Adverse Events Reports		
Statin	**Serious**	**Hepatotoxicity**	**Rhabdomyolysis**
Atorvastatin (373,549,063 prescriptions)	0.02% (13/7,314)	0.04% (7/1,689)	0.02% (2/839)
Simvastatin (162,523,229 prescriptions)	0.05% (17/3,681)	0.06% (6/938)	0.06% (8/1,273)
Pravastatin (90,806,652 prescriptions)	0.07% (9/1,377)	0.07% (3/441)	0.11% (2/188)
Lovastatin (33,655,661 prescriptions)	0% (0/252)	0% (0/78)	0% (0/97)

* Serious adverse events were defined as adverse events that were fatal, considered life-threatening by the reporter, or resulted in hospitalization.
Data are presented as percentage of AERs (number of adverse events with concomitant use of niacin-ER/total number of adverse events). Number of prescriptions dispensed during study period (1999 to March 31, 2005) is noted for each statin.

Concomitant use of niacin-ER in statin-associated adverse events reports was rare (range 0% to 1% of reports) for various types of adverse events considered. There was no difference among serious AE, hepatotoxicity, and rhabdomyolysis. From 1999 to March 2005, concomitant use of simvastatin and niacin-ER resulted in 0.05% serious adverse events, 0.06% hepatotoxicity, and 0.06% rhabdomyolysis. [9]

7 Alsheikh-Ali A. et al. Safety if Lovastatin/Extended Release Niacin Compared with Lovastatin Alone, Atorvastatin Alone, Pravastatin Alone and Simvastatin Alone. *American Journal of Cardiology*.2007; 99:379-381.

8 Ibid.
9 Ibid.

7.1.5 Common Adverse Events

7.1.5.1 Eliciting adverse events data in the development program

Adverse events were recorded in the case report forms (CRF) based on information volunteered by or elicited from the patient, or from examinations or evaluations made by the investigator or staff. Flushing events were recorded in self-reported "flushing logs" by the patient. Flushing was only considered an adverse event by the applicant if it resulted in discontinuation from the study or it satisfied at least one of the criteria for a serious adverse event.

7.1.5.2 Appropriateness of adverse event categorization and preferred terms

The applicant appears to have appropriately categorized the verbatim adverse event term used into the preferred term. The following table is an example of the AE text used compared to the preferred term.

Table 18: Categorization of Verbatim Term to Preferred Term

Categorization of Events		
Treatment Arm	**AE Text**	**Preferred Term**
NS 1000/20	calf muscle cramp	muscle cramp
NS 1000/20	neck pain	neck pain
NS 1000/20	left groin tenderness	groin pain
NS 1000/20	left knee pain	arthralgia
NS 1000/40	ganglion cyst, left hand	synovial cyst
NS 2000/20	heel (rt) discomfort	limb discomfort NOS
S80	intermittent stiff neck	musculoskeletal stiffness
S80	achniness in joints	arthralgia

7.1.5.3 Incidence of common adverse events

In the original NDA submission the Applicant stated there were 631 reported adverse events in the combined Simcor treatment arms (N= 403) and 343 adverse events in the combined simvastatin treatment arms (N=238).

This reviewer requested that the Applicant combine all reports of flushing as an adverse event, instead of only counting flushing as an AE if it was a serious adverse event or if it resulted in a discontinuation. With the inclusion of all reported flushing as an AE, the number of AEs increased to 4757 in the Simcor treatment arms and 1753 AEs in the simvastatin monotherapy arms. About 78.2% of patients who received Simcor reported any AEs compared to 72% in the simvastatin monotherapy (Tables 19-20).

Table 19: Summary of Treatment-Emergent AEs Including Flushing, Dose Group A

	Simvastatin 20mg N=114	Simcor 1000/20mg N=123	Simcor 2000/20mg N=64	Combined Simcor Group A N=187
# of adverse events (AEs)	723	1493	852	2345
Subjects				
Any AEs	71 (62.3%)	88 (71.5%)	52 (81.3%)	140 (74.9%)
Serious AEs	3 (2.6%)	2 (1.6%)	2 (3.1%)	4 (2.1%)
Withdrawals due to AEs	6 (5.3%)	16 (13.0%)	11 (17.2%)	27 (14.4%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Source: Table 5.1.1 Submission 0004 9/25/07

Table 20: Summary of Treatment-Emergent AEs Including Flushing, Dose Group B

	Simvastatin 80mg N=119	Simcor 1000/40mg N=116	Simcor 2000/40mg N=100	Combined Simcor Group B N=216
# of adverse events (AEs)	1013	1235	1177	2412
Subjects				
Any AEs	97 (81.5%)	91 (78.4%)	84 (84.0%)	175 (81.0%)
Serious AEs	2 (1.7%)	5 (4.3%)	2 (2.0%)	7 (3.2%)
Withdrawals due to AEs	8 (6.7%)	15 (12.9%)	13 (13.0%)	28 (13.0%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*Source: Table 5.1.2 from submission 0004 9/25/07

Table 21: Summary of Treatment-Emergent AEs Including Flushing –Overall

	Combined Simvastatin N=238	Simcor Combined Group A N=187	Simcor Combined Group B N=216	Simcor Overall (Groups A& B) N=403
# of adverse events (AEs)	1753	2345	2412	4757
Subjects				
Any AEs	171 (71.8%)	140 (74.9%)	175 (81.0%)	315 (78.2%)
Serious AEs	6 (2.5%)	4 (2.1%)	7 (3.2%)	11 (2.7%)
Withdrawals due to AEs	16 (6.7%)	27 (14.4%)	28 (13.0%)	55 (13.6%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

*Source: Table 5.1.3 from submission 0004 9/25/07

Reviewing the number of total number adverse events, it is clear that flushing events represent a major proportion of "total number of AEs". For example, the number of total AEs increased from 631 to 4,757 reports in the combined Simcor treatment arms.

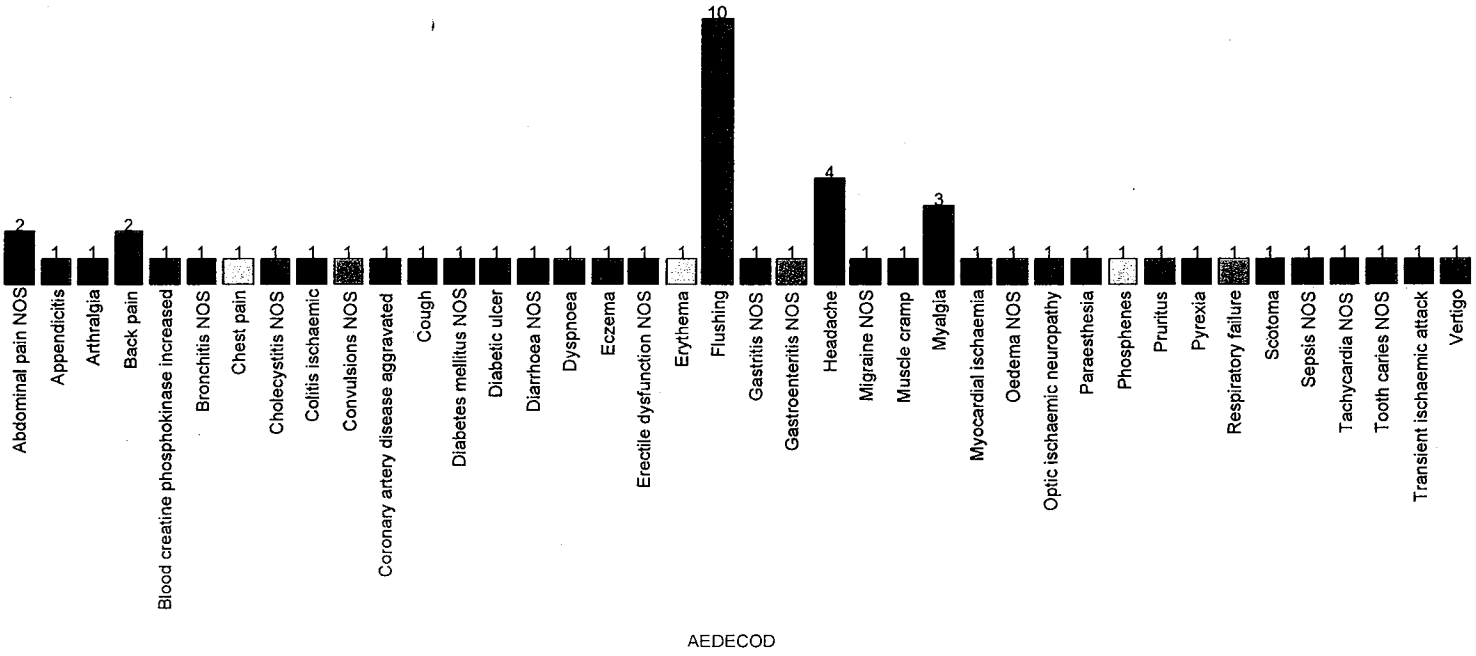
Adverse events were further categorized by intensity in the clinical trial as:

- **Mild**: Subject was aware of the event but easily tolerated it, and event did not cause any limitations to usual activities.
- **Moderate**: Event caused some limitation to subject's usual activities.
- **Severe**: Event caused inability for subject to carry out usual activities.

Approximately 40% of subjects reported AEs with mild intensity in the combined Simcor treatment arms as compared to 30% in the simvastatin combined treatment arms. Thirty-three percent of patients categorized their AE as moderate in intensity in both the combined Simcor arms and in the combined simvastatin arms. Severe AEs were reported by 8.4% of patients in the combined Simcor arms and 8.4% of patients in the combined simvastatin arms.

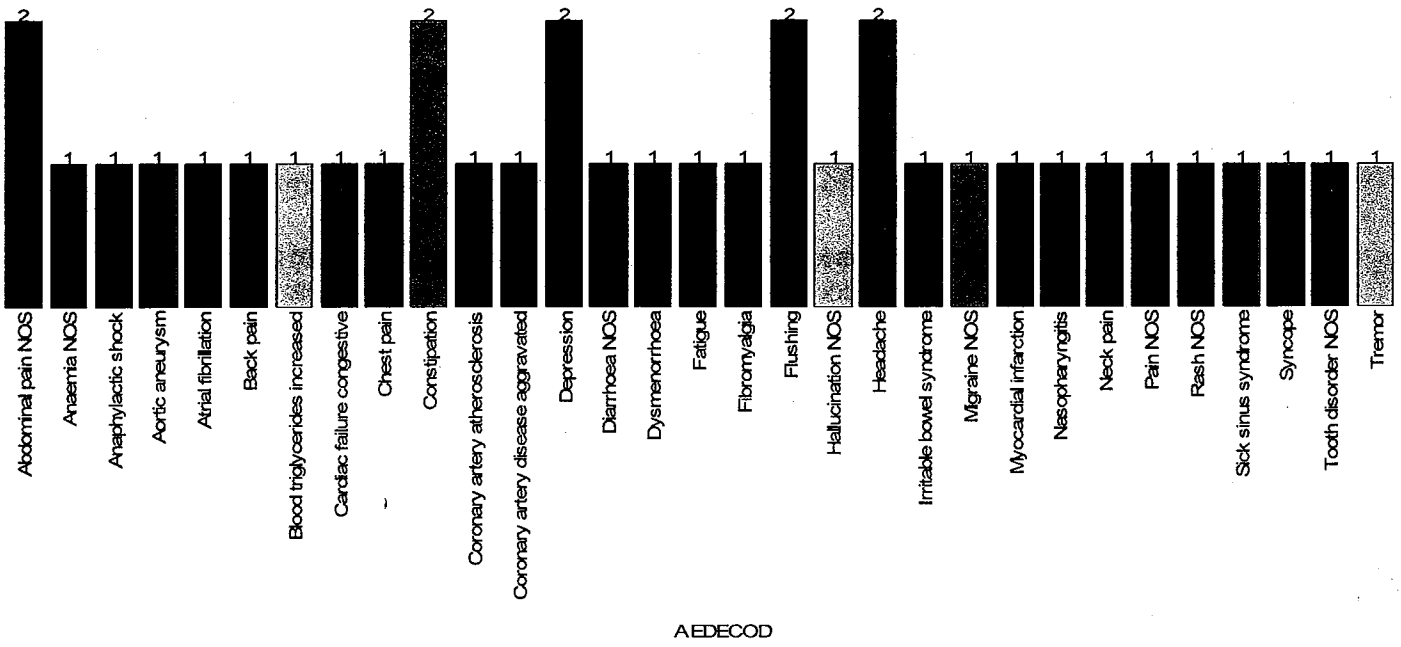
Flushing (vascular disorders) and headache (nervous system disorders) were most often reported as severe in the combined Simcor arms as compared to the simvastatin arms. The following bar graph shows the number of patients with severe AE by the preferred term.

Figure 3: Simcor Overall AE Identified as Severe



In the combined Simcor treatment arms, the adverse event overwhelmingly identified as severe was flushing (Figure 3). Headache and myalgia were a distant second. In contrast, the combined simvastatin treatment arms had a range of adverse events which were all identified as equally severe, including abdominal pain, constipation, depression, flushing, and headache (Figure 4).

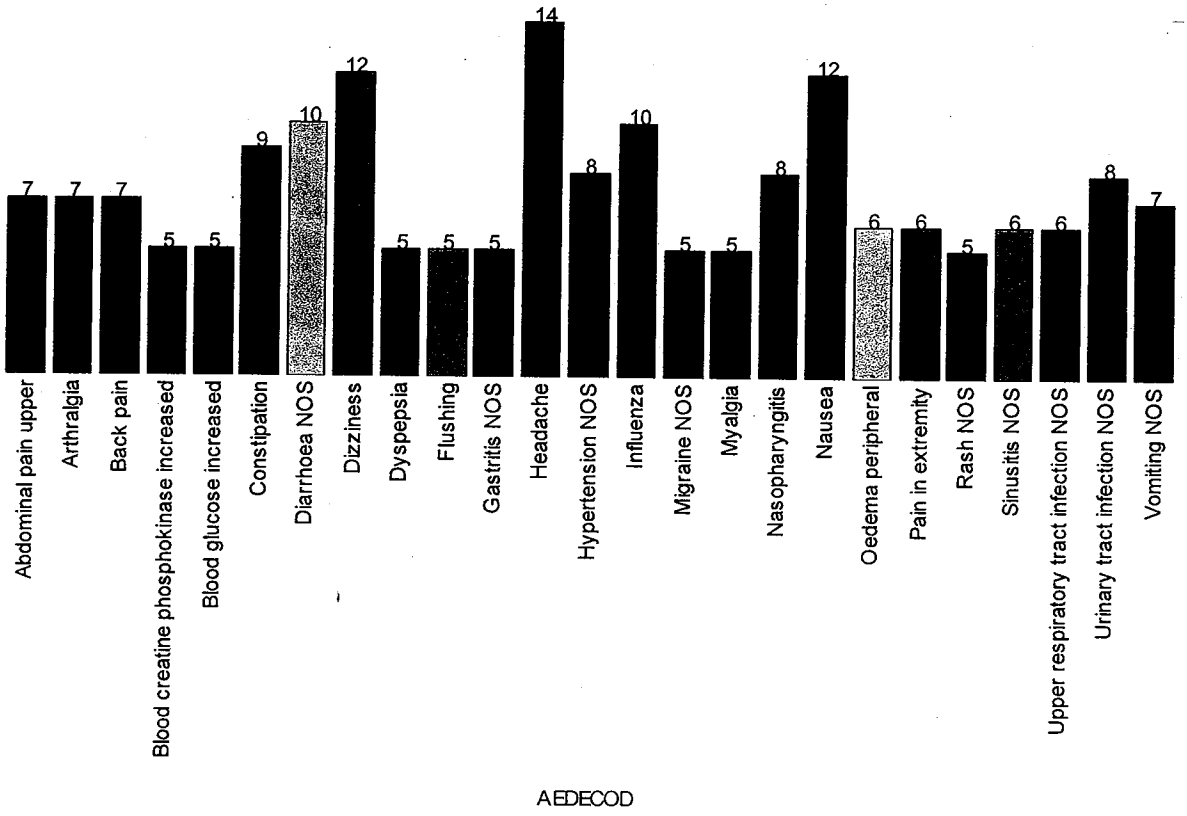
Figure 4: Simvastatin Overall AE Identified as Severe



7.1.5.4 Common adverse event tables

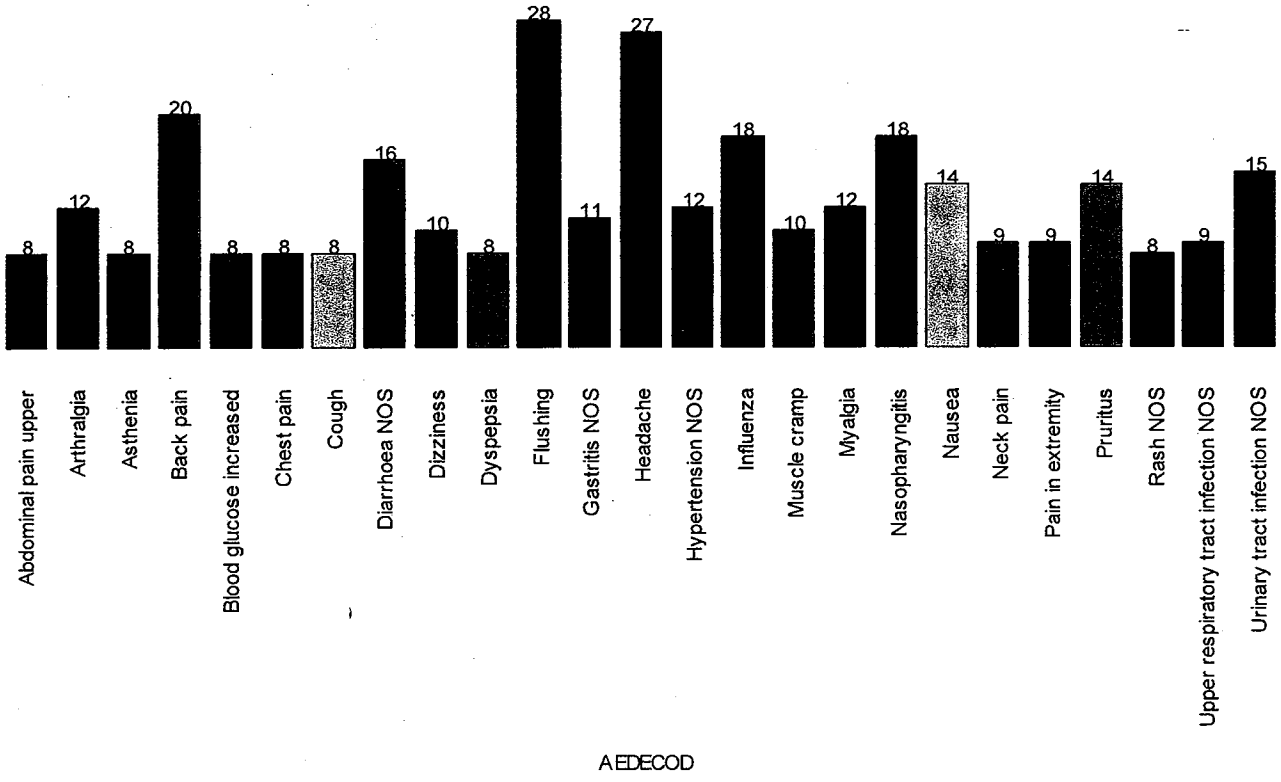
The most common treatment-emergent adverse event identified in the combined simvastatin groups were: headache, nausea, dizziness, and diarrhea (Figure 5). In comparison, the most common treatment-emergent adverse event in the combined Simcor groups were: flushing, headache, back pain, and nasopharyngitis (Figure 6).

Figure 5: Most Common Treatment Emergent AE (> 2%) in Simvastatin Overall Group



APPEARS THIS WAY
ON ORIGINAL

Figure 6: Most Common Treatment Emergent AE (> 2%) in Simcor Overall Group



7.1.5.5 Identifying common and drug-related adverse events

Flushing events were considered to be drug-related to the niacin component of Simcor. However, as an immediate-release niacin was given to the simvastatin only group, both the active control and the treatment group had some flushing (see section 7.1.3.3).

Myopathy and/or rhabdomyolysis have both been reported when simvastatin is used in combination with greater than one gram of niacin. In this controlled clinical trial, muscle-related adverse events were as follows in the combined Simcor treatment arms (N=403): myalgias=12 (3%), arthralgias=12 (3%), back pain=20 (5%), neck pain=9 (2%), muscle cramp=10 (2%), and pain in the extremity=9 (2%). Muscle-related adverse events in the combined simvastatin monotherapy arms (N=238) were as follows: myalgias=5 (2%), arthralgias=7 (3%), back pain=7 (3%) and pain in the extremity=6 (3%). Combining all of these AEs shows that were 17% muscle-related AEs for Simcor and 11% for simvastatin monotherapy.

7.1.5.6 Additional analyses and explorations

Adverse events were further analyzed by gender and race as shown in the following tables.

Table 22: Treatment Emergent AEs including flushing in Whites in Dose Group A

	S20 N=86	Simcor 1000/20 N=92	Simcor 2000/20 N=48	Simcor Overall N=1649
# of adverse events (AEs)	293	959	690	1649
Subjects				
Any AEs	48 (55.8%)	61 (66.3%)	39 (81.3%)	100 (71.4%)
Serious AEs	1 (1.2%)	1 (1.1%)	0 (0.0%)	1 (0.7%)
Withdrawals due to AEs	6 (7.0%)	9 (9.8%)	7 (14.6%)	16 (11.4%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 23: Treatment Emergent AEs including flushing in Non-Whites Dose Group A

	S20 N=28	Simcor 1000/20 N=31	Simcor 2000/20 N=16	Simcor Overall N=47
# of adverse events (AEs)	430	534	162	696
Subjects				
Any AEs	23 (82.1%)	27 (87.1%)	13 (81.3%)	40 (85.1%)
Serious AEs	2 (7.1%)	1 (3.2%)	2 (12.5%)	3 (6.4%)
Withdrawals due to AEs	0 (0.0%)	7 (22.6%)	4 (25.0%)	11 (23.4%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 24: Treatment Emergent AEs including flushing in Whites in Dose Group B

	S80 N=93	Simcor 1000/40 N=90	Simcor 2000/40 N=85	Simcor Overall N=175
# of adverse events (AEs)	821	933	893	1826
Subjects				
Any AEs	76 (81.7%)	71 (78.9%)	74 (87.1%)	145 (82.9%)
Serious AEs	2 (2.2%)	3 (3.3%)	1 (1.2%)	4 (2.3%)
Withdrawals due to AEs	5 (5.4%)	13 (14.4%)	12 (14.1%)	25 (14.3%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

Table 25: Treatment Emergent AEs including flushing in Non-Whites Dose Group B

	S80 N=26	Simcor 1000/40 N=26	Simcor 2000/40 N=15	Simcor Overall N=41
# of adverse events (AEs)	192	302	284	586
Subjects				
Any AEs	21 (80.8%)	20 (76.9%)	10 (66.7%)	30 (73.2%)
Serious AEs	0 (0.0%)	2 (7.7%)	1 (6.7%)	3 (7.3%)
Withdrawals due to AEs	3 (11.5%)	2 (7.7%)	1 (6.7%)	3 (7.3%)
Deaths	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)

The analysis of treatment emergent adverse events by race (White vs. non-Whites) shows that overall in Dose Group A, 71% of Whites had any AEs in the Simcor overall group compared to 85% of non-Whites who had any AEs. In Dose Group B, 82% of Whites had any AEs vs. 73% of non-Whites. Thus, there was no trend toward an association between race and treatment-emergent AEs in the two dose groups.

Females reported flushing AEs more often than men. An AE leading to discontinuation was reported by 16.6% of the females and 11.1% of the males in the Simcor overall group.

7.1.6 Less Common Adverse Events

There were no additional adverse events that altered the known adverse event profile of Simcor.

7.1.7 Laboratory Findings

There was no specific definition of a treatment-emergent laboratory abnormality (TELA) within the original NDA. This reviewer defined a TELA as any laboratory abnormality that worsened during study drug treatment regardless of baseline value. This is consistent with the ICH definition of an Adverse Event as "...any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product" [10]

7.1.7.1 Overview of laboratory testing in the development program

In SEACOAST, hematology and full chemistry screen (including liver function tests, fasting blood sugar, phosphorus, and CPK) and were obtained at screening and in the lipid qualification phase as well as on Weeks 4, 8, 12 and 24. Urinalysis was performed at screening and Weeks 4,8,12 and 24. HbA1C was obtained at screening, lipid qualification phase, and weeks 12 and 24. The following table shows the schedule of events for the safety laboratories.

[10] ICH Good Clinical Practice guidelines, Section II. Definitions and Terminology Associated with Clinical Safety Experience, Sept. 1997).

Table 26: Clinical Laboratory Studies Schedule of Events

	Screen	Run-in	Qual 1	Qual 2	Qual 3 - 41	Wk 0 Random	Wk 4	Wk 8	Wk 12	Wk 24 or Term
Clinical Laboratory Studies:										
Serum Basic Lipid Panel (Total-C, TG, LDL-C, HDL-C)2	X		X	X	X		X	X	X	X
Special Panel (Apo A-I, Apo B, Lp A-I, hs-CRP, etc.)2						X			X	X
Serum Chemistry2, 3, 4 (including										
Thyroid stimulating hormone [TSH] and T4)5	X			X			X	X	X	X
Whole Blood Hematology2	X			X		X	X	X	X	X
Plasma PT, PTT	X			X					X	X
Whole Blood HbA1C 2	X			X					X	X
Serum and Urine Pregnancy Test6	X			X						X
Urinalysis7	X						X	X	X	X
Reference Samples						X	X	X	X	X

7.1.7.2 Selection of studies and analyses for drug-control comparisons of laboratory values

SEACOAST was the only active-controlled study and therefore was the main focus of the safety review. However, the data from the longer, completed open-label study, OCEANS, and the ongoing open-label SUPREME trial have been reviewed to maximize our understanding of the long-term safety of the combination of simvastatin and niacin. The analysis is found in section 10.

7.1.7.3 Standard analyses and explorations of laboratory data

7.1.7.4 Analyses focused on measures of central tendency

Table 27: AST (IU/L) Changes from Baseline-Overall

Table 7.1.6A
AST (IU/L) Change From Baseline - Overall
Population: Safety

Treatment Arm	Statistic	Baseline	Change from Baseline			
			Week 4	Week 8	Week 12	Week 24
Simva Overall*	n	228	219	216	211	201
	Mean(SD)	19.7(5.3)	0.8(5.0)	1.1(5.3)	1.4(5.4)	0.5(5.4)
	Median	19.2	0.8	0.0	0.9	0.0
	Min,Max	10.0,45.0	-14.1,42.4	-12.5,41.5	-15.0,38.8	-22.9,26.5
NS Group A Overall	n	178	165	157	151	138
	Mean(SD)	19.0(5.1)	3.1(14.7)	1.8(5.2)	1.8(5.5)	1.9(5.9)
	Median	18.3	1.7	1.7	1.7	1.8
	Min,Max	9.7,35.8	-13.2,165.8	-11.7,26.7	-14.2,22.5	-12.5,45.0
NS Group B Overall	n	215	211	197	192	178
	Mean(SD)	20.3(5.7)	0.4(4.2)	1.1(4.7)	2.6(8.3)	1.9(5.1)
	Median	19.4	0.8	0.9	1.7	2.5
	Min,Max	10.6,42.4	-9.7,15.9	-9.7,26.5	-13.2,50.3	-22.9,15.0
NS Overall	n	393	376	354	343	316
	Mean(SD)	19.7(5.4)	1.6(10.3)	1.4(4.9)	2.3(7.2)	1.9(5.4)
	Median	18.5	0.9	0.9	1.7	1.8
	Min,Max	9.7,42.4	-13.2,165.8	-11.7,26.7	-14.2,50.3	-22.9,45.0

The mean change from baseline to end of treatment at Week 24 in AST for the simvastatin monotherapy was 0.5 IU (SD 5.4) compared to a mean change of 1.9 IU (SD 5.4) for the Simcor treatment arms. This reviewer does not consider the change from baseline to be a clinically meaningful difference between the treatment groups in AST.

Table 28: ALT (IU/L) Changes from Baseline-Overall

Table 7.1.12A
ALT (SGPT) (IU/L) Change From Baseline - Overall
Population: Safety

Treatment Arm	Statistic	Baseline	Change from Baseline			
			Week 4	Week 8	Week 12	Week 24
Simva Overall*	n	228	220	216	211	201
	Mean(SD)	24.5(9.0)	0.6(10.1)	1.3(8.8)	1.4(9.0)	-0.1(8.6)
	Median	23.5	0.0	0.0	0.0	-0.8
	Min,Max	9.2,53.7	-31.3,106.2	-19.8,56.3	-21.0,51.5	-23.5,42.0
NS Group A Overall	n	178	165	159	154	140
	Mean(SD)	25.5(9.7)	2.4(16.6)	0.5(9.1)	1.1(14.6)	-0.2(11.0)
	Median	23.4	0.0	0.0	0.0	-1.2
	Min,Max	9.8,51.8	-33.2,129.7	-23.4,37.1	-23.4,146.5	-31.3,65.8
NS Group B Overall	n	215	211	198	192	179
	Mean(SD)	23.5(9.8)	-0.1(6.7)	0.2(7.6)	1.5(11.5)	0.3(7.7)
	Median	21.0	0.0	0.0	0.0	0.8
	Min,Max	8.7,56.8	-30.9,28.8	-33.4,33.3	-28.4,65.8	-27.2,25.4
NS Overall	n	393	376	357	346	319
	Mean(SD)	24.4(9.8)	1.0(12.1)	0.3(8.3)	1.3(13.0)	0.1(9.3)
	Median	22.2	0.0	0.0	0.0	0.0
	Min,Max	8.7,56.8	-33.2,129.7	-33.4,37.1	-28.4,146.5	-31.3,65.8

The mean change from baseline to end of treatment at Week 24 in ALT for the simvastatin monotherapy was -0.1 IU (SD 8.6) compared to a mean change of 0.1 IU (SD 9.3) for the Simcor treatment arms. This reviewer does not consider the change from baseline to be a clinically meaningful difference between the treatment groups in ALT.

Table 29: CPK (IU/L) Changes from Baseline-Overall

Table 7.1.34A
CPK (CK) (IU/L), Total Change From Baseline - Overall
Population: Safety

Treatment Arm	Statistic	Baseline	Change from Baseline			
			Week 4	Week 8	Week 12	Week 24
Simva Overall*	n	228	221	217	211	201
	Mean(SD)	133.5(63.8)	11.5(73.7)	9.0(63.3)	24.5(226.2)	3.6(53.0)
	Median	120.4	4.6	4.5	7.2	1.8
	Min,Max	43.3,475.0	-323.1,699.3	-337.5,424.8	-333.0,3195.9	-303.3,207.4
NS Group A Overall	n	178	165	159	155	140
	Mean(SD)	129.3(58.4)	14.2(59.3)	23.1(65.5)	21.6(77.4)	33.0(88.5)
	Median	115.8	6.2	9.3	9.3	10.9
	Min,Max	50.8,331.0	-186.7,351.0	-150.1,392.4	-137.7,626.4	-150.1,672.3
NS Group B Overall	n	215	211	198	192	179
	Mean(SD)	136.4(70.4)	11.1(61.8)	10.4(56.5)	14.9(62.7)	17.6(64.4)
	Median	115.9	2.0	7.1	7.8	9.3
	Min,Max	42.4,499.6	-189.8,331.9	-121.5,510.7	-190.6,519.9	-198.4,424.8
NS Overall	n	393	376	357	347	319
	Mean(SD)	133.2(65.2)	12.5(60.7)	16.1(60.9)	17.9(69.6)	24.4(76.2)
	Median	115.8	3.4	7.9	8.5	10.8
	Min,Max	42.4,499.6	-189.8,351.0	-150.1,510.7	-190.6,626.4	-198.4,672.3

The changes in CPK are considerably different between the simvastatin monotherapy and Simcor treatment groups with the mean CPK difference from baseline for simvastatin of 3.6 IU (SD 53) and for Simcor 24.4 IU (SD 76).

Table 29 and 30 show the percent HbA1C change from baseline in Dose Group A and Dose Group B, respectively. In Dose Group A, the mean change for simvastatin 20mg was 0.1% (SD of 0.6%). For the Simcor 1000/20mg and 2000/20mg combined, the mean change from baseline was 0.2% (SD of 0.5%). In Dose Group B, the mean change for simvastatin 80mg was 0.3% (SD of 0.7%. For the Simcor treatment arms combined in Dose Group B, the mean change was 0.2% (SD 0.5).

Table 30: HgA1C (%) Change from Baseline –Dose Group A

Table 7.1.92A
HBA1C (%) Change From Baseline - Dose Group A
Population: Safety

Treatment Arm	Statistic	Baseline	Change from Baseline	
			Week 12	Week 24
S20	n	104	98	95
	Mean(SD)	6.9(0.8)	0.1(0.7)	0.1(0.6)
	Median	6.8	0.0	0.1
	Min,Max	5.4,10.1	-1.2,5.2	-1.4,2.6
NS 1000/20	n	108	94	87
	Mean(SD)	7.0(1.0)	0.3(0.7)	0.2(0.5)
	Median	6.8	0.2	0.1
	Min,Max	5.1,10.0	-0.9,5.2	-0.9,2.3
NS 2000/20	n	61	52	50
	Mean(SD)	6.9(0.8)	0.4(0.6)	0.2(0.5)
	Median	6.8	0.3	0.1
	Min,Max	5.6,9.3	-0.6,2.7	-0.6,1.6
NS Group A Overall	n	169	146	137
	Mean(SD)	7.0(0.9)	0.3(0.6)	0.2(0.5)
	Median	6.8	0.2	0.1
	Min,Max	5.1,10.0	-0.9,5.2	-0.9,2.3

Table 31: HbA1C (%) Change from Baseline-Dose Group B

Table 7.1.94A
HBA1C (%) Change From Baseline - Dose Group B
Population: Safety

Treatment Arm	Statistic	Baseline	Change from Baseline	
			Week 12	Week 24
S80	n	112	102	98
	Mean(SD)	7.0(0.9)	0.2(0.7)	0.3(0.7)
	Median	6.8	0.0	0.2
	Min,Max	5.4,10.6	-1.2,4.7	-1.2,3.8
NS 1000/40	n	114	99	91
	Mean(SD)	7.2(1.0)	0.3(0.7)	0.2(0.6)
	Median	7.0	0.1	0.2
	Min,Max	5.5,10.5	-1.2,2.7	-1.9,2.6
NS 2000/40	n	98	93	87
	Mean(SD)	7.2(0.9)	0.2(0.4)	0.2(0.4)
	Median	6.9	0.2	0.2
	Min,Max	6.0,10.1	-2.1,1.5	-1.4,1.1
NS Group B Overall	n	212	192	178
	Mean(SD)	7.2(1.0)	0.2(0.6)	0.2(0.5)
	Median	7.0	0.2	0.2
	Min,Max	5.5,10.5	-2.1,2.7	-1.9,2.6

There were no consistent differences between Simcor and simvastatin for PT, uric acid, phosphorous, and only a small reduction in platelet count was observed for Simcor compared with simvastatin (the highest change occurred in the NS 2000/40 arm [-13.8 K/mm^3 compared to -1.1 K/mm^3 for S80]).

7.1.7.4.1 Analyses focused on outliers or shifts from normal to abnormal

7.1.7.4.1.1 Muscle biochemistry

Mild CPK elevations less than 3X ULN occurred in about 30% of patients taking Simcor study drugs and 27% of patients taking only simvastatin. Seven patients (1.7%) from the Simcor Overall group had a CPK elevation between 3X ULN and 5X ULN as compared with one patient (0.4%) in the simvastatin overall group. No patients had CPK between 5X and 10X ULN. One patient had a one time elevation 10X ULN. No patients discontinued due to CPK abnormalities and there were no reported cases of myopathy. The following table shows the incidence of CPK elevations.

Table 32: Incidence of CPK Elevations

	Number (%) of Patients			
	Simvastatin Overall N=238	Simcor Group A N=187	Simcor Group B N=216	Combined Simcor (Groups A& B) N=403
>ULN and ≤3.0 x ULN	65 (27.3)	55 (29.4)	69 (31.9)	124 (30.8)
>3.0 x ULN and ≤5.0 x ULN	1 (0.4)	4 (2.1)	3 (1.4)	7 (1.7)
>5.0 x ULN and ≤10.0 x ULN	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
>10.0 x ULN	1 (0.4)	0 (0.0)	0 (0.0)	0 (0.0)

CPK elevations >10 X ULN occurred in only one patient (90517) treated with S80. The patient was reported to have been exercising prior to the blood draw. A repeat test showed that his CPK value had returned to baseline and remained at baseline until completion of the study.

The minimum and maximum change from baseline to Week 24 in CPK values for simvastatin monotherapy was -303.3 and +207.4 IU/L. The minimum and maximum change from baseline to Week 24 in CPK values for Simcor was -198.4 and +672.3.

7.1.7.4.1.2 Hepatic biochemistry

The following two tables show the incidence of AST and ALT elevation in the Safety population. No treatment arm had any patient with two consecutive AST elevations greater than 3X ULN. However, a total of 79 (20%) patients in the Simcor treatment arms had AST greater than normal compared to 29 (12.2%) of patients in the simvastatin treatment arms. Two patients who received Simcor 1000/20mg had AST >3XULN at 104 u/L and 108 u/L.

Table 33: Incidence of AST Elevations

Table 7.2.3
AST Abnormalities - Overall
Population: Safety

Category	Treatment: Simva Overall* (N=238)	NS Group A Overall (N=187)	NS Group B Overall (N=216)	NS Overall (N=403)
At least 2 consecutive values > 3.0x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
> ULN	29 (12.2%)	35 (18.7%)	44 (20.4%)	79 (19.6%)
> 1.3x ULN	9 (3.8%)	11 (5.9%)	15 (6.9%)	26 (6.5%)
> 2.0x ULN	2 (0.8%)	3 (1.6%)	2 (0.9%)	5 (1.2%)
> 3.0x ULN	0 (0.0%)	2 (1.1%)	0 (0.0%)	2 (0.5%)
> ULN and <= 1.3x ULN	20 (8.4%)	24 (12.8%)	29 (13.4%)	53 (13.2%)
> 1.3x ULN and <= 2.0x ULN	7 (2.9%)	8 (4.3%)	13 (6.0%)	21 (5.2%)
> 2.0x ULN and <= 3.0x ULN	2 (0.8%)	1 (0.5%)	2 (0.9%)	3 (0.7%)

Table 34: Incidence of ALT Elevations

Table 7.2.6
ALT Abnormalities - Overall
Population: Safety

Category	Treatment: Simva Overall* (N=238)	NS Group A Overall (N=187)	NS Group B Overall (N=216)	NS Overall (N=403)
At least 2 consecutive values > 3.0x ULN	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
> ULN	33 (13.9%)	31 (16.6%)	26 (12.0%)	57 (14.1%)
> 1.3x ULN	12 (5.0%)	10 (5.3%)	11 (5.1%)	21 (5.2%)
> 2.0x ULN	1 (0.4%)	4 (2.1%)	2 (0.9%)	6 (1.5%)
> 3.0x ULN	1 (0.4%)	3 (1.6%)	0 (0.0%)	3 (0.7%)
> ULN and <= 1.3x ULN	21 (8.8%)	21 (11.2%)	15 (6.9%)	36 (8.9%)
> 1.3x ULN and <= 2.0x ULN	11 (4.6%)	6 (3.2%)	9 (4.2%)	15 (3.7%)
> 2.0x ULN and <= 3.0x ULN	0 (0.0%)	1 (0.5%)	2 (0.9%)	3 (0.7%)

No patient had two consecutive elevations of ALT greater than 3XULN in any of the treatment groups. However, 57 (14.4%) of patients who received Simcor had an abnormal ALT compared to 33 (13.9%) of patients who received simvastatin monotherapy. Three patients who received Simcor (two on 1000/20mg and one on 2000/20mg) had an ALT elevation greater than 3XULN. One patient who received simvastatin 80mg had an ALT elevation greater than 3XULN. The highest ALT value was 148 u/L.

7.1.7.3.1.3 Fasting Blood Sugars

Table 34 shows various statistics for fasting blood glucose (FBG) for the entire Safety population. Although the mean FBG in the simvastatin arms and the Simcor arms were similar, the maximum recorded FBG at Week 24 in the simvastatin monotherapy was 386.7 mg/dl as compared to 411.9 mg/dl in the Simcor Overall treatment arms.

Table 35: Fasting Blood Glucose for Safety Population

Table 7.4.1A
Glucose, Fasting (mg/dL), Total Normalized Observed Values - Overall Population: Safety

Treatment Arm	Statistic	Baseline	Week 4	Week 8	Week 12	Week 24
Simva Overall*	n	227	221	217	211	201
	Mean(SD)	141.0(32.5)	141.5(39.9)	146.5(41.0)	145.6(48.0)	149.5(47.0)
	Median	131.9	129.4	134.4	131.9	134.4
	Min,Max	94.1,278.2	61.7,495.1	96.6,381.6	58.7,489.6	99.1,386.7
NS Group A Overall	n	178	165	159	155	140
	Mean(SD)	143.0(36.3)	148.8(42.5)	155.9(60.6)	154.1(50.0)	147.9(39.5)
	Median	134.4	136.0	138.3	140.5	139.5
	Min,Max	71.4,283.2	94.1,343.2	99.1,527.9	93.2,392.8	99.1,411.9
NS Group B Overall	n	214	211	197	192	179
	Mean(SD)	149.1(43.1)	157.6(48.6)	160.5(51.3)	159.4(55.4)	150.0(43.5)
	Median	136.9	142.0	144.5	140.7	139.5
	Min,Max	66.3,305.9	93.2,464.9	76.4,376.6	73.0,472.4	68.5,353.9
NS Overall	n	392	376	356	347	319
	Mean(SD)	146.3(40.2)	153.8(46.2)	158.4(55.6)	157.0(53.0)	149.0(41.8)
	Median	136.0	139.5	142.0	140.5	139.5
	Min,Max	66.3,305.9	93.2,464.9	76.4,527.9	73.0,472.4	68.5,411.9

7.1.7.3.1.3 Other laboratory values

There were no instances of elevations > 2X ULN in uric acid or LDH. There was one patient who had an elevated total bilirubin up to 2XULN in the NS 2000/40 arm. Two patients in the NS 1000/20 arm and one patient in the 1000/40 arm had elevations up to 2XULN in alkaline phosphatase. Five patients had an elevated prothrombin time (PT) up to 2XULN and one patient had a PT up to 3XULN; none of these patients had accompanying clinical signs of bleeding.

7.1.8 Vital Signs

7.1.8.1 Overview of vital signs testing in the development program

Per protocol, vital sign testing (which included heart rate, systolic and diastolic blood pressure, and weight) was performed at each visit during both the placebo and lipid qualification period.

There were no meaningful changes in vital signs and weight from baseline to end of study in any treatment arm in either dose group.

7.1.9 Electrocardiograms (ECGs)

Not pertinent to this submission.

7.1.10 Immunogenicity

Not pertinent to this submission.

7.1.11 Human Carcinogenicity

Not pertinent to this submission.

7.1.12 Special Safety Studies

Not applicable to this submission.

7.1.13 Withdrawal Phenomena and/or Abuse Potential

Not applicable to this submission.

7.1.14 Human Reproduction and Pregnancy Data

No new data was presented in this submission. Simvastatin in a Pregnancy Category X.

7.1.15 Assessment of Effect on Growth

Not applicable to this submission.

7.1.16 Overdose Experience

There is no specific treatment in the event of overdoses with simvastatin or niacin ER. In the event of overdose, the patient is to be treated symptomatically and supportive measures instituted as required. Hemodialysis does not significantly enhance the clearance of simvastatin.

7.1.17 Postmarketing Experience

The Office of Surveillance and Epidemiology assessed physicians' intentions for concurrent product use for simvastatin/Zocor with Niaspan®. The following review conclusion and tables are from a report by Dr. Borders-Hemphill. From 2002-2006, concurrent product use between simvastatin/Zocor® and Niaspan® represented around f all simvastatin/Zocor® occurrences and close to f Niaspan® occurrences.

Simvastatir trengths were reported as being issued more times by office-based physicians than any other simvastatin/Zocor® strength from 2002-2006. A greater proportion of the simvastatin/Zocor® strengths reported as being issued with Niaspan® as the concurrent product compared to the other strengths of simvastatin/Zocor®.

Niaspan® as reported more times as being issued by office-based physicians than the other Niaspan® strengths from 2002-2006. A greater proportion of ng was reported as being issued with simvastatin/Zocor® compared to the other strengths of Niaspan®.

Table 36: The number of times Niaspan® has been reported as being used together with various strengths of simvastatin (brand and generic)

Projected Number of Total Drug Occurrences [1] (*In Thousands, add 3 zeros*) by Concurrent Products [2] (Niaspan® used with simvastatin by strength) Reported from Office-Based Physician Practices in the U.S., 2002-2006

	2002		2003		2004		2005		2006	
	Occur.	*Share*	Occur.	*Share*	Occur.	*Share*	Occur.	*Share*	Occur.	*Share*
Simvastatin (brand/generic)										
20 MG Niaspan®										
40 MG Niaspan®										
10 MG Niaspan®										
80 MG Niaspan®										
5 MG Niaspan®										
UNSPEC. Niaspan®										

--- means no data; a zero means less than 500 total projected
[1] The projected number of times a product is issued regardless of diagnosis.
[2] A drug occurrence can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.
[3] A concurrent product is defined as when 2 or more products are used together, regardless of condition treated
Verispan, Physician Drug and Diagnosis Audit (PDDA), Years 2002 - 2006, Extracted 8-21-07.
Source file: 2007-1782 PDDA 8-21-07 simv niasp conc prod.qry

Table 37: The number of times simvastatin and/or Zocor® has been reported as being used together with various strengths of Niaspan®.

Projected Number of Total Drug Occurrences – (*In Thousands, add 3 zeros*) by Concurrent Products (simvastatin/Zocor used with Niaspan by strength) Reported from Office Based Physician Practices in the U.S., 2002-2006

	2002		2003		2004		2005		2006	
	Occur	***Share***	**Occur**	***Share***	**Occur**	***Share***	**Occur**	***Share***	**Occur**	***Share***
Niaspan										
500 MG Zocor®										
1000 MG Zocor®										
750 MG Zocor® Simvastatin										
UNSPEC. Zocor®										

The projected number of times a product is used regardless of diagnosis.
A drug occurrence can result from a prescription written, a sample given, a recommendation for OTC products, recommendation with sample, a product dispensed or administered in the office, a hospital order, a nursing home order or a combination of these.
A concurrent product is defined as when 2 or more products are used together regardless of condition treated.
Verispan Physician Drug and Diagnosis Audit (PDDA), Years 2002 - 2006 Extracted 8-21-07 Source file: 2007-1782 PDDA 8-21-07 simv niasp conc prod.qry

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

The Simcor development program for the indication of primary hypercholesterolemia , mixed dyslipidemia, and hypertriglyceridemia included three Phase 1 studies (Studies CP-03-012004, 019-03-04-CP, and 019-04-05-CP) and two Phase 3 studies (SEACOAST and OCEANS). In these studies, Simcor was administered to a total of 1041 subjects: 129 healthy adults and 912 adults with primary type II hyperlipidemia, mixed dyslipidemia, or hypertriglyceridemia (see table below from applicant submission).

Table 38: Summary of Patients in the Simcor Development Program

			Number of Patients Treated		
Development Phase	**Subject Population**	**Number of Studies**	**Simcor**	**Simvastatin Alone**	**Total**

			Number of Patients Treated		
Development Phase	Subject Population	Number of Studies	Simcor	Simvastatin Alone	Total
Phase 1	Healthy Adults	3	129	42	130[a]
Phase 3	Primary type II hyperlipidemia or mixed dyslipidemia	2	912	238	1150
Total		5	1041	280	1280

a. These were crossover studies and the number of patients in each treatment group does not add up to the total number treated.

For analysis of the extent of patient exposure in SEACOAST, the overall mean time patients were on study medication was 143.7 days for Simcor Overall and 150.8 days for Simvastatin Overall. The majority of patients (64-75%) treated with simvastatin or with Simcor in each dose group had duration of treatment of at least 161 days. This reviewer requested additional exposure data by the four different Simcor dosage strengths from the applicant. The following tables display those data.

Table 39: Extent of Exposure Dose Group A

Table 3.1
Extent of Exposure to Study Medication - Dose Group A
Population: Safety

	Statistic	S20 (N=114)	NS 1000/20 (N=123)	NS 2000/20 (N=64)	NS Group A Overall (N=187)
Days on Randomized Study Medication	Mean (SD)	154.7 (42.7)	138.4 (54.0)	139.9 (52.2)	138.9 (53.3)
	Median	169.0	166.0	167.5	167.0
	Min, Max	8.0, 201.0	3.0, 211.0	8.0, 196.0	3.0, 211.0
Duration of Treatment					
< 28 days	n (%)	5 (4.4%)	6 (4.9%)	4 (6.3%)	10 (5.3%)
>=28 days	n (%)	109 (95.6%)	113 (91.9%)	60 (93.8%)	173 (92.5%)
>=56 days	n (%)	106 (93.0%)	102 (82.9%)	56 (87.5%)	158 (84.5%)
>=84 days	n (%)	103 (90.4%)	94 (76.4%)	53 (82.8%)	147 (78.6%)
>=112 days	n (%)	101 (88.6%)	89 (72.4%)	49 (76.6%)	138 (73.8%)
>=140 days	n (%)	100 (87.7%)	86 (69.9%)	47 (73.4%)	133 (71.1%)
>=161 days	n (%)	87 (76.3%)	78 (63.4%)	42 (65.6%)	120 (64.2%)
>=168 days	n (%)	64 (56.1%)	54 (43.9%)	32 (50.0%)	86 (46.0%)

In Dose Group A, the average number of days for the different treatment arms was as follows:

- Simcor 1000/20mg was 138 days (19.7 weeks)
- Simcor 2000/20mg was 140 days (20 weeks)
- Simvastatin 20 mg was 155 days. (22 weeks)

Table 40: Extent of Exposure Dose Group B

Table 3.2
Extent of Exposure to Study Medication - Dose Group B
Population: Safety

	Statistic	S80 (N=119)	NS 1000/40 (N=116)	NS 2000/40 (N=100)	NS Group B Overall (N=216)
Days on Randomized Study Medication	Mean (SD)	148.6 (47.7)	144.6 (51.7)	151.3 (40.3)	147.7 (46.8)
	Median	168.0	167.0	168.0	167.0
	Min, Max	1.0, 198.0	3.0, 199.0	4.0, 187.0	3.0, 199.0
Duration of Treatment					
< 28 days	n (%)	6 (5.0%)	6 (5.2%)	1 (1.0%)	7 (3.2%)
>=28 days	n (%)	111 (93.3%)	110 (94.8%)	99 (99.0%)	209 (96.8%)
>=56 days	n (%)	104 (87.4%)	103 (88.8%)	94 (94.0%)	197 (91.2%)
>=84 days	n (%)	100 (84.0%)	96 (82.8%)	91 (91.0%)	187 (86.6%)
>=112 days	n (%)	99 (83.2%)	94 (81.0%)	85 (85.0%)	179 (82.9%)
>=140 days	n (%)	96 (80.7%)	92 (79.3%)	81 (81.0%)	173 (80.1%)
>=161 days	n (%)	91 (76.5%)	82 (70.7%)	77 (77.0%)	159 (73.6%)
>=168 days	n (%)	60 (50.4%)	50 (43.1%)	55 (55.0%)	105 (48.6%)

In Dose Group B, the average number of days patients was on the different treatment arms were as follows:

- Simcor 1000/40mg was 145 days (20.7 weeks)
- Simcor 2000/40mg was 151 days (21.5 weeks)
- Simvastatin 80mg was 149 days (21.2 weeks)

Table 41: Extent of Exposure Safety Population

Table 3.3
Extent of Exposure to Study Medication - Overall
Population: Safety

	Statistic	Simva Overall* (N=238)	NS Group A Overall (N=187)	NS Group B Overall (N=216)	NS Overall (N=403)
Days on Randomized Study Medication	Mean (SD)	150.8 (45.8)	138.9 (53.3)	147.7 (46.8)	143.7 (50.0)
	Median	168.0	167.0	167.0	167.0
	Min, Max	1.0, 201.0	3.0, 211.0	3.0, 199.0	3.0, 211.0
Duration of Treatment					
< 28 days	n (%)	11 (4.6%)	10 (5.3%)	7 (3.2%)	17 (4.2%)
>=28 days	n (%)	225 (94.5%)	173 (92.5%)	209 (96.8%)	382 (94.8%)
>=56 days	n (%)	214 (89.9%)	158 (84.5%)	197 (91.2%)	355 (88.1%)
>=84 days	n (%)	207 (87.0%)	147 (78.6%)	187 (86.6%)	334 (82.9%)
>=112 days	n (%)	203 (85.3%)	138 (73.8%)	179 (82.9%)	317 (78.7%)
>=140 days	n (%)	198 (83.2%)	133 (71.1%)	173 (80.1%)	306 (75.9%)
>=161 days	n (%)	180 (75.6%)	120 (64.2%)	159 (73.6%)	279 (69.2%)
>=168 days	n (%)	126 (52.9%)	86 (46.0%)	105 (48.6%)	191 (47.4%)

In SEACOAST, approximately 47.4% or 191 patients who received any dose of Simcor remained on the treatment for at least 24 weeks or 6 months.

7.2.1.1 Study type and design/patient enumeration

A total of 4007 patients were screened for SEACOAST. Of those screened, 3,345 were withdrawn and 662 completed screening. All patients completing the screening period were randomized to either Dose Group A (319) or Dose Group B (343). The overall percentage of

patients who discontinued during the study was 26%. In Dose Group A, there were more discontinuations in the treatment arms receiving Simcor than simvastatin monotherapy (23.5% vs. 8.8%). In Dose Group B, the discontinuations between the Simcor treatment arms and the simvastatin monotherapy arm were similar (19% Simcor vs. 15% simvastatin).[11]

This was an international study with 129 sites in 5 countries. The majority of subjects were randomized to study treatments in the US (43%; 281/657), Argentina (24%; 158/657); or Russia (21%; 137/657). At the time Russia entered the study, Dose B had completed enrollment. Thus, Russia did not participate in Dose B enrollment.

7.2.1.2 Demographics

Table 42 presents the demographic and baseline characteristics for Dose Group A . Across the treatment arms, patients were similar at baseline in terms of demographics and general characteristics. Approximately half of the patients were men, the majority was White, and the mean age ranged from 54.2-57.4 years at screening. Overall, 49 (15.6%) subjects in Dose Group A were lipid treatment-naïve at randomization. More than half of the patients within each treatment arm were in the CHD and CHD risk equivalent risk category, and nearly a quarter had diabetes.

Table 42: Demographics and baseline characteristics- Dose Group A randomized patients

BASELINE CHARACTERISTIC SUMMARY STATISTIC	S20 N=121	NS 1000/20 N=127	NS 2000/20 N=66	NS GROUP A OVERALL N=193
Age				
Mean (SD)	57.4 (10.2)	55.5 (10.4)	54.2 (10.5)	55.1 (10.4)
Min, max	32, 76	30, 81	34, 75	30, 81
Age group				
21 – 64 [N (%)]	87 (71.9)	100 (78.7)	54 (81.8)	154 (79.8)
≥ 65 [N (%)]	34 (28.1)	27 (21.3)	12 (18.2)	39 (20.2)
Sex				
Male [N (%)]	59 (48.8)	62 (48.8)	38 (57.6)	100 (51.8)
Female [N (%)]	62 (51.2)	65 (51.2)	28 (42.4)	93 (48.2)
BMI (kg/m^2)				
Mean (SD)	29.3 (5.6)	29 (5.4)	31.4 (10)	29.8 (7.3)
Min, max	19, 53	14, 53	19, 77	14, 77
CHD Risk Category				
CHD and CHD risk equivalent	70 (57.9)	74 (58.3)	36 (54.5)	110 (57)
	42 (34.7)	36 (28.3)	20 (30.3)	56 (29)
≥2 risk factors	9 (7.4)	17 (13.4)	10 (15.2)	27 (14)

11 Discontinuations are based on the number in m-ITT population.

BASELINE CHARACTERISTIC SUMMARY STATISTIC	S20 N=121	NS 1000/20 N=127	NS 2000/20 N=66	NS GROUP A OVERALL N=193
0-1 risk factors				
Race				
Caucasian [N (%)]	91 (75.2)	95 (74.8)	50 (75.8)	145 (75.1)
Black [N (%)]	1 (0.8)	1 (0.8)	0 (0)	1 (0.5)
Asian [N (%)]	0 (0)	2 (1.6)	1 (1.5)	3 (1.6)
Hispanic [N (%)]	29 (24)	27 (21.3)	13 (19.7)	40 (20.7)
Other [N (%)]	0 (0)	2 (1.6)	2 (3.0)	4 (2.1)
Lipid Medication Status at randomization [N (%)]				
Naïve	13 (10.7)	20 (15.7)	16 (24.2)	36 (18.7)
Non-naïve	108 (89.3)	107 (84.3)	50 (75.8)	157 (81.3)

Table 43 presents the demographic and baseline characteristics for Dose Group B. Across the treatment arms, subjects were similar at baseline in terms of demographics and general characteristics. More than half of the subjects were male, the majority were White, and the mean age ranged from 59.7-61.3 years at screening. Greater than 75% of the subjects within each treatment arm were in the CHD and CHD risk equivalent risk category, and more than a third had diabetes.

Table 43: : Demographics and baseline characteristics- Dose Group B randomized patients

BASELINE CHARACTERISTIC SUMMARY STATISTIC	S80 N=123	NS 1000/40 N=118	NS 2000/40 N=102	NS GROUP B OVERALL N=220
Age				
Mean (SD)	61.3 (10.6)	60.1 (10.8)	59.7 (8.5)	59.9 (9.8)
Min, max	36, 88	32, 83	42, 82	32, 83
Age group				
21 – 64 [N (%)]	74 (60.2)	74 (62.7)	73 (71.6)	147 (66.8)
≥ 65 [N (%)]	49 (39.8)	44 (37.3)	29 (28.4)	73 (33.2)
Sex				
Male [N (%)]	63 (51.2)	62 (52.5)	62 (60.8)	124 (56.4)
Female [N (%)]	60 (48.8)	56 (47.5)	40 (39.2)	96 (43.6)
BMI (kg/m^2)				
Mean (SD)	30.2 (6.2)	30.5 (5.7)	29.8 (4.7)	30.2 (5.3)
Min, max	20, 47.7	20.8, 54.2	20.2, 45	20.2, 54.2
CHD Risk Category				
	94 (76.4)	92 (78.0)	77 (75.5)	169 (76.8)

BASELINE CHARACTERISTIC SUMMARY STATISTIC	S80 N=123	NS 1000/40 N=118	NS 2000/40 N=102	NS GROUP B OVERALL N=220
CHD and CHD risk equivalent	27 (22)	23 (19.5)	22 (21.6)	45 (20.5)
≥2 risk factors	2 (1.6)	3 (2.5)	3 (2.9)	6 (2.7)
0-1 risk factors				
Race				
Caucasian [N (%)]	96 (78)	92 (78)	87 (85.3)	179 (81.4)
Black [N (%)]	11 (8.9)	13 (11)	5 (4.9)	18 (8.2)
Asian [N (%)]	0 (0)	1 (0.8)	0 (0)	1 (0.5)
Hispanic [N (%)]	15 (12.2)	12 (10.2)	10 (9.8)	22 (10)
Other [N (%)]	1 (0.8)	0 (0)	0 (0)	0 (0)

Lipid Characteristics

Table 44 below presents a summary of the baseline lipid characteristics for Dose Group A at study entry. Overall, baseline lipid values were generally similar across the treatment arms. Mean non-HDL-C (160-164 mg/dL) and LDL-C (117-121 mg/dL) levels were moderately elevated at baseline. Mean TG levels across the treatment arms (206-217 mg/dL) ranged from the upper end of the borderline high range to the high range. Mean non-HDL-C values were more than 30 mg/dL higher than LDL-C values for each of the treatment arms, reflecting the contribution of relatively high TG levels. Median HDL-C levels were 42.8-43.7 mg/dL.

Table 44: SEACOAST Dose Group A mean baseline lipids and lipoproteins

	SIMVASTATIN 20 MG (N=121)	SIMCOR 1000/20 (N=127)	SIMCOR 2000/20 (N=66)
Non-HDL-C	160.6	164.2	161.4
LDL-C	118.9	121.6	117.6
TC	204.3	207.9	204.2
HDL-C	43.7	43.7	42.8
TG	206.0	217.4	215.8
Apo B	101.6	102.7	99.7

Table 45 presents a summary of the baseline lipid characteristics for Dose Group B at study entry. Overall, baseline lipid values were generally similar across the treatment arms. Mean non-HDL-C (134-144 mg/dL) and LDL-C 102-110.7 mg/dL) levels were only mildly elevated at baseline. Mean TG levels across the treatment arms (157-168 mg/dL) ranged from the upper end of the normal range to the lower end of the borderline range. Mean non-HDL-C values were approximately 30 mg/dL higher than LDL-C values for each of the treatment arms, consistent with a population with LDL-C elevation as the predominant lipid abnormality. Mean HDL-C levels were 46.8-47.8 mg/dL.

Table 45: SEACOAST Dose Group B mean baseline lipids and lipoproteins

	SIMVASTATIN 80 MG (N=123)	SIMCOR 1000/40 (N=118)	SIMCOR 2000/40 (N=102)
Non-HDL-C	134.4	140.8	144.3
LDL-C	102.7	109.4	110.7
TC	182.3	187.7	191.4
HDL-C	47.8	46.8	47.0
TG	159.0	157.4	168.3
Apo B	90.0	93.0	94.3

7.2.1.3 Extent of exposure (dose/duration)

The extent of exposure to Simcor at the 4 different doses used in the SEACOAST trial were requested from the applicant. The planned study duration was 24 weeks of double-blind treatment, after a 6 week open-label simvastatin lead-in period. The mean number of days for any exposure to Simcor at any dose was 144 days. The mean number of days for any exposure to simvastatin only at any dose was 151 days.

7.2.2 Description of Secondary Clinical Data Sources Used to Evaluate Safety

The following other sources were searched for safety issues associated with the concurrent use of simvastatin and niacin: the medical literature and the AERS database.

For a discussion of the results of the results of the review of the AERS database, please see Section 7.1.4.

For a discussion of the medical literature, please see Section 8.6.

7.2.2.1 Other studies

Other studies as they pertain to combination of simvastatin and niacin-ER and the safety profile of theses drugs have been presented throughout this document and used for comparison purposes.

7.2.2.2 Postmarketing experience

See Section 7.1.4

7.2.2.3 Literature

See Section 8.6

7.2.3 Adequacy of Overall Clinical Experience

The overall clinical experience with Simcor is adequate given that both components of this combination product have been available by prescription for decades. The safety profile of simvastatin and Niaspan are well known. The safety findings in both the controlled and uncontrolled clinical studies submitted with this NDA suggest that Simcor is relatively safe for chronic administration.

The study design reflected the Agency's requirement that the lipid-modifying effects of Simcor be assessed only in patients who failed to meet NCEP target (or options) for non-HDL-C after adequate treatment with simvastatin monotherapy (20 mg and/or 40 mg). The Agency indicated a second study starting with niacin and adding simvastatin would not be necessary. However, in this clinical reviewer's opinion, the omission of the niacin monotherapy arm means that the study does not support conclusions about the efficacy of the combination product compared with niacin monotherapy.

The applicant is proposing Simcor as a product of convenience, however one of the studied doses (2000/20mg) is not offered as a single tablet. Instead, patients will have to take two tablets: one Simcor and another Niaspan. In this reviewer's opinion, this is contrary to the purpose of a combination product.

7.2.4 Adequacy of Special Animal and/or In Vitro Testing

Both niacin extended release (ER) and simvastatin are approved drugs as Niaspan® (NDA 20-381) and Zocor® (NDA 19-766). Extensive nonclinical studies have been conducted with the approved Zocor®. No nonclinical pharmacology/toxicology studies have been conducted with Simcor, but there is extensive clinical experience with both drugs in humans.

7.2.5 Adequacy of Routine Clinical Testing

Overall, routine efforts to monitor safety laboratories and vital signs were adequate. However, the effort to elicit flushing as an adverse event was disappointing. By only counting flushing as an adverse event if it led to discontinuation or was a serious adverse event diminished the accuracy of adverse events monitoring.

7.2.6 Assessment of Quality and Completeness of Data

The applicant presented the safety data in a manner consistent with center guidelines and in a manner previously agreed to by the Division. The clinical sections of the NDA were organized in a manner to allow adequate review.

7.2.7 Additional Submissions, Including Safety Update

A 4-month safety update on an ongoing trial, SUPREME, was submitted to the NDA. As there was no ISS in the original NDA, this safety update was not pooled, See Appendix C for a safety review of the 4-month update from SUPREME.

7.3 Summary of Selected Drug-Related Adverse Events, Important Limitations of Data, and Conclusions

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle, e.g., uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with simvastatin. Furthermore, myopathy and/or rhabdomyolysis have been reported when simvastatin is used in combination with $\geq$ 1 gram/day of niacin. This reviewer recommends prominent warning/precautions for the Simcor package insert.

Persistent elevations in hepatic transaminases can occur. This reviewer recommends prominent warnings for Simcor in the package insert.

Treatment-related increases in HbA1C with Simcor has been shown in the trials submitted with this NDA. This is a known adverse effect of niacin. This reviewer recommends precautionary language in the label to closely monitor diabetic or potentially diabetic patients on Simcor.

Niacin ER has been associated with dose-related reductions in platelet count. In the controlled clinical trial submitted with this NDA, the mean percent change from baseline for patients treated with 2000/40mg was -5.6%

Niacin ER has been associated with small increases of prothrombin time. In a submitted study with Simcor, this effect was not seen.

Niacin ER has been associated with increases in uric acid; however, this effect was not seen in the submitted clinical trial.

Niacin ER has been associated with small dose-related reductions in phosphorous levels. This effect was not seen with the submitted trial.

In this reviewer's opinion all the treatment-related adverse effects should be included in the package insert.

7.4 General Methodology

7.4.1 Pooling Data Across Studies to Estimate and Compare Incidence

To support the efficacy of Simcor in modifying lipid and lipoprotein levels, only data from SEACOST was considered relevant as this was the controlled trial. Due to the different methodologies employed in the other study, pooling of the data was not possible.

8 ADDITIONAL CLINICAL ISSUES

8.1 Dosing Regimen and Administration

The Division of Clinical Pharmacology also reviewed the acceptability of the three strengths of Simcor:1000/20mg, 750/20mg, and 500/20mg. According to the clinical pharmacology reviewer, the 1000/20mg and 500/20mg tablet strengths of Simcor are acceptable based on the relative bioavailability studies and Phase 3 clinical trials. However, the 750/20mg was not utilized in any clinical pharmacology study nor qualified for a biowaiver.

This clinical reviewer requested efficacy and safety data from the Applicant regarding the 750/20mg dose. In their response, the Applicant reiterated that the 750/20mg dose was used in the titration schedule in the OCEANS study. The Applicant identified three patients in OCEANS who could not tolerate the 2000/40mg dose and had to be back titrated to 1500/40mg. Review of laboratory, adverse events and efficacy data for those three patients did not reveal any safety signals.

Although there is limited use of the 750 mg/20 mg tablet strength during the OCEANS study, this reviewer believes that this dosage strength will be used in clinical practice as a titration to higher doses, as advised in the currently-approved Niaspan® label and as provided in the proposed Simcor label. The therapeutic effects with niacin ER is generally attained with doses greater than 1 gram daily. It is anticipated that patients will receive the 750 mg/20 mg Simcor tablets during the titration phase of the treatment, for a period of approximately four weeks, since the therapeutic targets for most patients require higher maintenance doses of Niaspan®.

This clinical reviewer agrees with the argument that there should be very little difference in safety, efficacy, and tolerability during this short period compared to that observed for the corresponding Niaspan® formulation dose strength, since the ——— does not affect the bioavailability of the ———

8.2 Drug-Drug Interactions

No drug interaction studies were conducted with Simcor. The following drug-drug interactions were commented on in the current submission.

- **Cyclosporine:** *Although the mechanism is not fully understood, cyclosporine has been shown to increase the area under the curve (AUC) of HMG-CoA reductase inhibitors. The increase in AUC for simvastatin acid is presumably due in part, to inhibition of CYP3A4. The risk of myopathy/rhabdomyolysis is increased by concomitant administration of cyclosporine or danazol particularly with higher doses of simvastatin.*

Two patients in the 2000/40mg Simcor treatment arm of SEACOAST received concomitant cyclosporine. One of these patients (MI02-021) had an AE of diarrhea 101 days after start of study drug. The other patient (NY04-021) had urticaria (Day 8), dysgeusia (Day 8), stomach discomfort (Day 35), eyelid disorder (Day 39), and contusion (Day 150).

- **Verapamil:** *The risk of myopathy/rhabdomyolysis is increased by concomitant administration of verapamil with higher doses of simvastatin.*

Three patients in the 1000/20mg Simcor treatment arm of Seacoast received concomitant verapamil. One of these patients (CL04-079) reported oral candidiasis (Day 59), gastritis (Day 79), and nausea (Day 119). A second patient (CL06-102) reported gastritis (Day 116) and influenza (Day 153). A third patient (M001-018) reported proteinuria (Day 29), hyperglycaemia (Day 57), fall (Day 75) and thrombocythaemia (Day 88). .

8.3 Special Populations

A summary of the special populations highlighted in the current Simcor label is provided, along with data from the SEACOAST study:

- *Data from the clinical trials suggest that women have a greater hypolipidemic response than men at equivalent doses of niacin extended-release. No consistent gender differences in efficacy and safety were observed in Simcor studies.*

According to the statistical reviewer, women in Dose Group A who took Simcor had more favorable response in non-HDL and LDL, on average, than men. However, the lipid responses were sensitive to the statistical analysis method. The sensitivity reflects the greater proportion of study drop-outs among women compared with men in Dose Group A. Because the LOCF imputation tends to reflect less non-HDL and LDL lowering in patients who did not complete the study, the difference in response between men and women is less when estimated from the ANCOVA/LOCF model than when estimated from the MMRM model. (please see Table 24 in Dr. Janice Derr's review).

The disproportion of study dropouts by gender was not as marked in Dose Group B as in Dose Group A. The effect of gender in the comparisons between the Simcor arms and the simvastatin 80mg arms was not as marked. Thus, this reviewer agrees with the applicant's summary that gender had some effects on certain lipid parameters, but this effect was not consistent.

- *There were 281 (30.8%) patients aged 65 and older treated with SIMCOR in Phase III clinical studies. No overall differences in safety and effectiveness were observed between these patients and younger patients, but greater sensitivity of some older individuals cannot be ruled out. A pharmacokinetic study with simvastatin showed the mean plasma level of HMG-CoA reductase inhibitory activity to be approximately 45% higher in elderly patients between 70-78years of age compared with patients 18-30 years of age.*

The effect of Simcor on non-HDL-C, LDL-C, HDL-C, Total-C, TG, and Lp(a) was generally consistent patients aged 65 and older and those younger than 65.

8.4 Pediatrics

In discussions with the Pediatric Regulatory Committee, the Division has granted the Applicant their requested pediatric waiver

8.5 Advisory Committee Meeting

Not applicable to this submission.

8.6 Literature Review

The current National Cholesterol Education Program (NECP) guidelines continue to recommend LDL-C as the primary target of cholesterol lowering therapy and to recommend therapy initiation with a single agent. Intensification of drug therapy either by increasing the dose or by combining a statin with another drug should be undertaken only if LDL goal has not been achieved. According to the guidelines, combination therapies are to be considered in patients whose LDL-C is at goal, but who have elevated TG. Non-HDL-C is the secondary target for risk reduction, after the primary target of LDL-C. [12]

Recently, clinical trials have shown that in some patients, LDL-C lowering alone is insufficient to optimize cardiovascular heart disease management. For example, in the Pravastatin or Atorvastatin Evaluation and Infection Trial (PROVE-IT) comparing atorvastatin 80mg vs. pravastatin 40mg in patients hospitalized for an acute coronary syndrome, the 2-year risk for a major CV event, among atorvastatin-treated patients, who achieved a mean on-trial LDL-C of

12 Third Report of the National Cholesterol Education Program (NECP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult treatment panel III) final report. *Circulation. 2002; 106;3143-421.*

63mg/dL was 22%. For the endpoint of death or MI, the 2-year event rate in the atorvastatin group was 8%. Extrapolated over a 10-year period, the risk for death or MI would be as high as 40% in this group, despite having a mean LDL-C of 62 mg/dL. Thus, the residual risk for a cardiovascular event remains high even after a reduction of LDL-C with a statin monotherapy.[13]

A literature review shows that there is growing number of patients with the metabolic syndrome (a combination of increased TG, low HDL-C, and insulin resistance and increased waist circumference). Based on the Third National Health and Nutrition Examination Survey (NHANES), the estimated overall prevalence of the metabolic syndrome in the US is 24% which corresponds to about 47 million people.[14]

Results from the VA-HIT trial show that raising low levels of HDL-C in CHD patients with normal LDL-C levels is associated with reductions in coronary events.[15] More recently, the HDL Atherosclerosis Treatment Study (HATS) has shown that treatment of the total lipid profile with a combination of simvastatin and niacin was associated with a significant regression of coronary atherosclerosis and further reductions in clinical events.[16]

Thus, although LDL-C remains the primary target of cholesterol lowering therapy, there is evidence that reducing non-HDL-C is also important in the management of cardiovascular disease.

8.7 Postmarketing Risk Management Plan

The adverse event profiles of simvastatin and niacin-extended release are well known. The Division will monitor prescription rates and AERS reports for Simcor post-approval. Particular attention will be paid to reports of serious muscle toxicity.

8.8 Other Relevant Materials

A consult was requested from the Division of Medication Error and Technical Support (DMETS) to assess if the proposed name, Simcor, could potentially be confused with other proprietary or established names. The results of the Proprietary Name Risk Assessment found that the proposed name, Simcor, has some similarity to other proprietary and established drug names, but the findings of the Failure Mode and Effect Analysis (FMEA) process indicate that the proposed name does not appear to be vulnerable to name confusion that could lead to medication errors. Thus, DMETS has no objections to the use of the proprietary name, Simcor.

---

13 Cannon, CP, Braunwald E, McCabe CH, et al. Comparison of intensive and moderate lipid lowering with statins after acute coronary syndromes. *N Engl J Med.*;2004;350:15.
14 Brunzell JD. Dyslipidemia of the metabolic syndrome. In:Eckel R, ed. *Obesity: Mechanisms and Clinical Management.* New York: Lippincott Williams &Wilkins;2002:378-398.
15 Rubins HB, Robins SJ, Collins D, Iranmanesh A et al. Distribution of lipids in 8500 men with coronary artery disease. Department of Veterans Affairs HDL Intervention Trial Study Group. *Am J Cardiol.* 1995;75:1196-201.
16 Brown BG, Zhao XQ, Chait A, et al. Simvastatin and Niacin, antioxidant vitamins, or the combination for the prevention of coronary disease. *N Engl J MED.* 2001; 345:1583-92.

9 OVERALL ASSESSMENT

9.1 Conclusions

Increasing evidence indicates optimizing cardiovascular disease management requires both LDL-C lowering and reduction of non-HDL-C. In this reviewer's opinion, when treatment with simvastatin monotherapy or niacin ER is inadequate, SIMCOR may be indicated to improve lipid parameters.

In theory, combination therapy can provide more effective coverage of the entire lipid profile. Although Simcor did reduce LDL-C, the submitted trial in this NDA did not show as favorable a modification as compared to simvastatin monotherapy. Simcor was superior for reducing TG, Apo B and raising HDL-C as compared to simvastatin monotherapy.

Although Simcor is effective in modifying lipid profiles, only outcome trials will provide conclusive evidence for cardiovascular disease management. A large controlled clinical trial known as **A**therothrombosis **I**nterventions in **M**etabolic Syndrome with Low HDL/**H**igh Triglyceride and **I**mpact on **G**lobal **H**ealth (AIM-HIGH) is examining whether the addition of niacin ER to simvastatin reduces the risk of cardiovascular morbidity and mortality compared to simvastatin alone in patients with low HDL-C and high TG. Results are expected in 2012.

Given the evidence at hand, this reviewer believes that Simcor will be a reasonable addition in the clinician's armamentarium. For this reason, this reviewer recommends approval.

9.2 Recommendation on Regulatory Action

It is recommended that Simcor be approved for the following indication: To reduce total-C, LDL-C, non-HDL-C, Apo B, and TG, and to increase HDL-C in patients with primary hypercholesterolemia, mixed dyslipidemia when treatment with simvastatin monotherapy or niacin extended-release is considered inadequate.

Simcor is also recommended for use in patients with hypertriglyceridemia (Fredrickson type IV) to reduce TG when treatment with simvastatin monotherapy and niacin monotherapy is considered inadequate.

9.3 Recommendation on Postmarketing Actions

The need for outcomes trials is emphasized by this clinical reviewer. Although either agent alone has been shown to have beneficial effects on cardiovascular morbidity and mortality, the outcomes trials of the two agents in combination is needed to provide conclusive evidence. AIM-HIGH should provide substantial evidence in that regard. This trial will randomize [redacted] patients with established vascular disease and atherogenic dyslipidemia to either simvastatin or a combination of niacin ER and simvastatin. These patients will be followed for a median of 4 years to see if combination therapy delays the time to a first major cardiovascular disease event.

9.3.1 Risk Management Activity

Simvastatin and niacin extended release have been available by prescription for many years and the adverse events profile of these agents are well known. Myopathy/ rhabdomyolysis signals will be followed in addition to the other known safety signals. The Division will monitor prescription rates and AERS reports for Simcor post approval.

9.3.2 Required Phase 4 Commitments

None.

9.3.3 Other Phase 4 Requests

None.

9.4 Labeling Review

As Simcor will be the first combination of a HMG CoA reductase inhibitor and niacin ER to be in a Physician Labeling Rule format, a detailed labeling review will be conducted separately from this document.

9.5 Comments to Applicant

As with other HMG-CoA reductase inhibitors, effects on skeletal muscle, e.g., uncomplicated myalgia, myopathy and, rarely, rhabdomyolysis, have been reported in patients treated with simvastatin. There have also been reports of myopathy and/or rhabdomyolysis when simvastatin is used in combination with $\geq$1 gram/day of niacin. This reviewer is concerned with the potential increase in myopathy/rhabdomyolysis. The Applicant should be advised to closely monitor utilization of Simcor and myopathy/rhabdomyolysis following approval of this NDA.

Use of niacin extended-release (ER) and simvastatin have been associated with abnormal liver tests. Although there were no persistent increases to more than 3X the upper limit of normal in serum transaminases in the submitted clinical trials for this NDA, the Applicant should be advised to continue monitoring for liver abnormalities following approval of Simcor.

Use of niacin ER has also been associated with a rise in fasting blood sugar. The effect on fasting blood glucose with the use of Simcor is of concern. The open-label study submitted with this NDA also shows an increase in glycosylated hemoglobin in patients taking Simcor. The applicant should be advised to monitor for impaired glucose tolerance incidence post-approval.

10 APPENDICES

10.1 Review of Individual Study Reports

10.1.2 Appendix A
Study: 019-01-03-CR: SEACOAST

The Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients with Dyslipidemia: A Dose-Ranging Study

Study initiation date: May 17, 2004
Study completion date: September 25, 2006

10.1.2.1 **Objectives**
Primary
The primary objective of the study was to assess the effects of different doses of Simcor® (NS) for 24 weeks on non-HDL-C. In Dose Group A, two doses of Simcor® (1000/20 mg and 2000/20 mg) were compared to monotherapy with simvastatin 20 mg (S20). In Dose Group B, two doses of Simcor® (2000/20 mg and 2000/40 mg) were compared to monotherapy with simvastatin 80 mg (S80).

Secondary
The secondary objectives of the study were to assess the effects of Simcor for 24 weeks on the following variables: LDL-C, HDL-C, TC, TG, and LP(a). Other secondary variables were apolipoprotein A-I, high-sensitivity C-reactive protein, lipoprotein A-1, TC to HDL-C ratio, LDL-C to HDL-C ratio and lipoprotein A-I to lipoprotein A-II ratio.

Safety was assessed by evaluations of vital signs, adverse events (AEs), clinical laboratory analyses, and electrocardiograms (ECGS).

10.1.2.2 **Endpoints**
Primary efficacy measures
The primary endpoint for SEACOAST was change from baseline values to end of treatment in non-HDL-C.

Secondary efficacy measures
Secondary efficacy endpoints were change in LDL-C, HDL-C, TC, TG, and LP(a) from baseline values to end of treatment. Other secondary variables were changes from baseline to end of treatment in apolipoprotein A-I, high-sensitivity C-reactive protein, lipoprotein A-1, TC to HDL-C ratio, LDL-C to HDL-C ratio and lipoprotein A-I to lipoprotein A-II ratio.

Safety and tolerability were measured by evaluating the incidence and severity of AEs, abnormal laboratory values (hematology, clinical chemistry, urinalysis), vital signs, and weight, ECGs, and physical exams. The adverse event of flushing was recorded in self-reported flushing logs.

10.1.2.3 **Statistical and Analytical Plans**

Analysis population: The following analysis sets were defined and used in the analysis and/or presentation of data:

- **Modified-Intention-to-Treat (m-ITT) population:** The modified intention to treat population consisted of all subjects contributing a baseline and at least one post baseline efficacy measurement. The m-ITT population excluded data from RU-02 site.
- **Per-Protocol (PP) population:** The PP population consisted of patients in the ITT population who were not major protocol violators or major deviators.
- **Safety Population:** The randomized subjects who took at least one dose of study medication.

In this study, subjects were randomized into Dose Group A (who either received S20, Simcor 1000/20 or Simcor 1000/40) and Dose Group B (who either received S80, Simcor 2000/20 or Simcor 2000/40). Primary hypothesis testing for the two groups were conducted separately, with a primary superiority hypothesis used for Dose Group A and a primary non-inferiority hypothesis used for Dose Group B.

In Dose Group A, the mean non-HDL-C percent change from baseline to Week 24 of the S20 arm was compared against that of the NS 2000/20 arm. Superiority of NS 2000/20 over S20 was concluded if NS 2000/20 was significantly better than S20 in lowering non-HDL-C. If this first test was significant, then the mean non-HDL-C percent change from baseline to Week 24 of the S20 arm was compared against that of the NS 1000/20 arm. Superiority of NS 1000/20 over S20 was concluded if NS 1000/20 was significantly better than S20 in lowering non-HDL-C. All tests were at the 2-sided α =0.05 level. Percent changes from baseline to Week 24 for all other efficacy endpoints were tested for superiority of NS vs. simvastatin, as above.

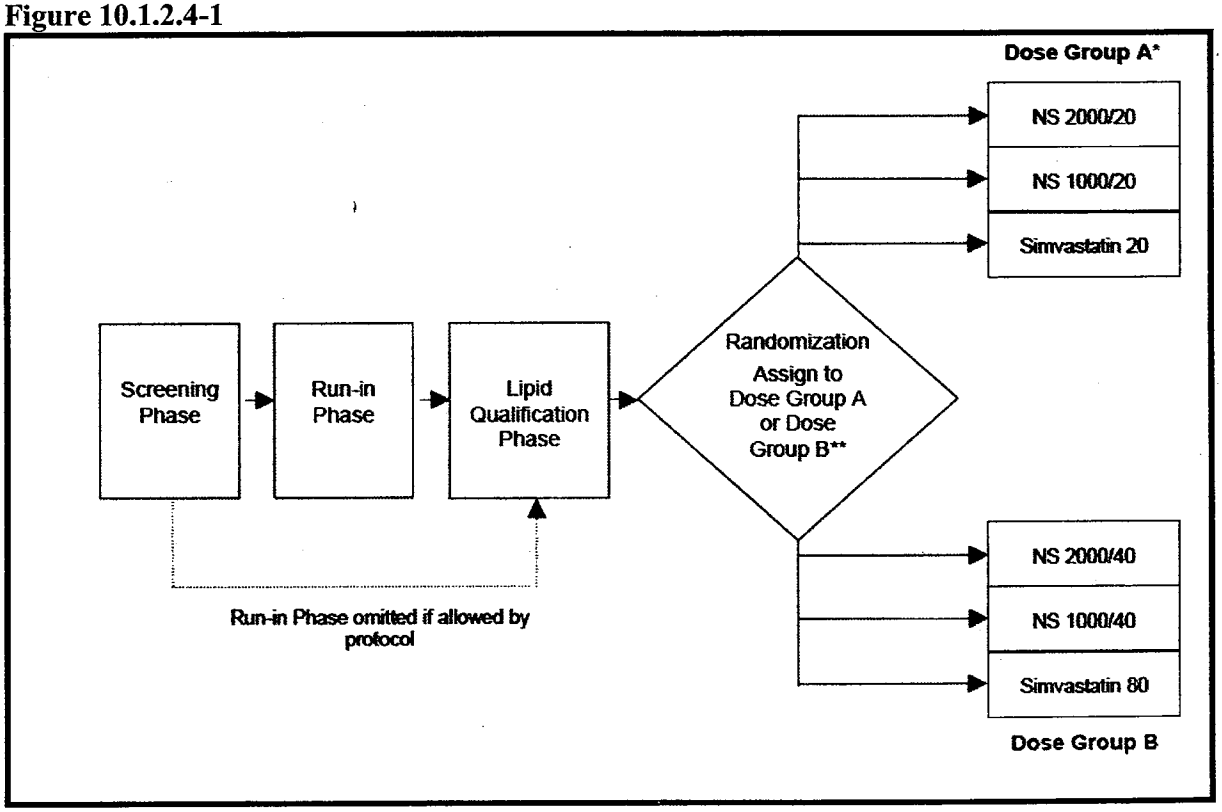
In Dose Group B, a 2-sided 95% confidence interval (CI) for the mean difference in non-HDL-C percent change from baseline to Week 24 between the NS 2000/40 and S80 treatment arms (NS 2000/40 – S80) was computed. Non-inferiority of NS 2000/40 relative to S80 was concluded if the upper bound of the 95% CI was $\leq$6%. If non-inferiority was concluded in the first test, then a 2-sided 95% CI for the mean difference in non-HDL-C percent change from baseline to Week 24 between the NS 1000/40 and S80 treatment arms was computed to test for noninferiority of NS 1000/40 relative to S80.

This closed testing procedure preserved the overall Type I error rate for testing the primary non-inferiority hypothesis. For any NS dose (NS 2000/40 and/or NS 1000/40) for which non-inferiority relative to S80 was concluded, superiority relative to S80 was also tested at the 2-sided α =0.05 level. The percent change from baseline to Week 24 for LDL-C was also tested in

a similar manner. Percent changes from baseline to Week 24 for all other efficacy endpoints were tested for superiority of NS vs. Simvastatin as in Dose Group A.

10.1.2.4 Study design: This was a 24-week, double-blind, active-controlled study of 641 patients randomized into either Dose Group A or Dose Group B depending on their non-HDL-C and LDL-C levels as well as prior treatment history. The study design reflected the Agency's requirement that the lipid-modifying effects of combination NS therapy be assessed only in patients who failed to meet NCEP target (or options) for non-HDL-C after adequate treatment with simvastatin monotherapy (20 mg and/or 40 mg). Thus, Dosing Group A randomized patients with elevated non-HDL-C with at-goal LDL-C and Dosing Group B randomized patients with elevated non-HDL-C regardless of LDL-C goal status. Non-HDL-C and LDL-C criteria were based either on NCEP-III Treatment Options or Goals. The figure below from the original NDA submission summarizes the SEACOAST study design.

Figure 10.1.2.4-1



Dose Group A had 3 arms: simvastatin 20 mg (S20), Simcor® 1000/20 mg (NS 1000/20), or Simcor® 2000/20 mg (NS 2000/40). Dose Group B had 3 arms: simvastatin 80 mg (S80), Simcor® 1000/40 mg (NS 1000/40), or Simcor® (NS 2000/40). Eligible subjects went through a screening phase, a 2 week Run-In phase, 1-4 week Lipid Qualification Phase, and a 24 week treatment phase with Simcor® (NS).

At screening, laboratory tests, physical examination, and medical history were obtained. Non-HDL and LDL criteria were based first on NCEP treatment options, then based on NCEP treatment goals with a change to protocol (Amendment #4).

If patients had both elevated non-HDL and LDL and were:

- treatment naïve or
- were previously taking statin equivalent to S20 mg or
- were taking non-statin lipid-modifying medications

then, patients were entered into Run-In with S20 mg for $\geq$ 2 weeks.

If patients had elevated non-HDL and had *at-goal LDL* and were treatment naïve or were previously on S20 mg for $\geq$ 2 weeks, then they were exempted from the Run-In and went directly to the Lipid Qualification Phase.

If patients had both elevated non-HDL and LDL and were

- taking statin therapy equivalent to S40 mg prior to study entry or
- had received S20 at the Lipid Qualification Phase and still had elevated LDL as well as an elevated non-HDL

then, patients were entered into Run-In with S40 mg for > 2 weeks.

If patients were taking S40 mg for > 2 weeks prior to the study and non-HDL was elevated, regardless of LDL, then they went straight into the Lipid Qualification Phase.

The purpose of the Lipid Qualification Phase was to determine whether the subject's average non-HDL-C level remained elevated for their CHD risk category and whether the variability between the 2 non-HDL-C levels was within 15%. If the variability between 2 consecutive visits was > 15%, third and/or fourth Qualification Visits were permitted. Patients were excluded from the study if non-HDL-C was at goal at the end of the Lipid Qualification.

The original study design included both an S20 and an S40 arm in Dose Group A. Amendment #3 to the protocol eliminated the S40 arm as no efficacy comparisons were going to be made with that treatment arm. Five patients had been randomized to the S40 arm before the amendment; those patients are considered in the safety review, but their data were not included in the efficacy review.

During the screening process, the applicant finished enrollment of the Dose B Group before Dose Group A. Protocol amendment #4 introduced a change to the screening process for Dose Group A. According to this amendment, treatment-naïve subjects at study entry had to have LDL-C levels within pre-specified limits; following simvastatin 20 mg run-in, they were eligible to be assigned to Dose Group A if their non-HDL-C levels remained elevated, regardless of their LDL-C levels. (See Amendment to Protocol # 4)

Randomization:
At the end of the Lipid Qualification Phase, patients who satisfied the entry criteria to Dose Group A and were either treatment naïve or had received S20 (either prior to study entry or during Run-In) were randomized into one of three arms. Patients assigned to Dose Group B and had received S40 mg (either prior to study or during the Run-In) were randomized into one of three arms.

Under the original protocols and Amendments #1-2, patients in Dose Group A were randomized in a 1:1:1:1 ratio to S20, S40, NS 1000/20, and NS 2000/20 and patients in Dose Group B were randomized in a 1:1:1 ratio to S80, NS 1000/40, and NS 2000/40. As part of the changes in Amendment #3, S40 was dropped from the study and the randomization ratio was changed to 2:2:1 to S20, NS 1000/20, and NS 2000/20 for Dose Group A and 3:3:2 for Dose Group B.

However, this change was applied going forward, and a small number had already enrolled in Dose Group A and a significant number of patients had already enrolled in Dose Group B. The final sample sizes are approximately 4:4:3 for Dose Group A and 3:3:2 for Dose Group B.

Treatments Administered:
Details and specific descriptions of the tablets used during the Double-Blind Treatment Phase are provided in Table . According to the applicant, patients in the simvastatin groups received niacin immediate-release (IR) 50 mg to assist in maintaining the study blind, as this dose induces flushing.

Table 10.1.2.4-2

Tablets Used in SEACOAST Double-Blind Treatment Phase

Abbreviation	Description
Tablets Matching NS 500/20 in Size and Appearance (blue-colored, coded with KOS on 1 side and 021 on the other)	
NS 500/20	Niacin ER 500 mg with simvastatin 20 mg
500/0	Niacin ER 500 mg
500P	Placebo tablet
500C/20	Control tablet of Niacin IR 50 mg with simvastatin 20 mg
500P/20	Placebo with simvastatin 20 mg
Tablets Matching NS 1000/20 in Size and Appearance (blue-colored, coded with KOS on 1 side and 023 on the other)	
NS 1000/20	Niacin ER 1000 mg with simvastatin 20 mg
1000/0	Niacin ER 1000 mg
1000P	Placebo tablet
1000C/20	Control tablet of Niacin IR 50 mg with simvastatin 20 mg
1000P/20	Placebo with simvastatin 20 mg

Tables 10.1.2.4-3 and 10.1.2.4-4

Dose Titration Regimen and Tablet Combinations – Dose Group A

Treatment	Treatment Phase (daily dose [mg], and tablet combination to achieve the dose)			
	Weeks 1-4	Weeks 5-8	Weeks 9-12	Weeks 13-24
S20[a,b]	**20** 1×500C/20 1×500P	**20** 1×500C/20 1×500P	**20** 1×500C/20 2×500P	**20** 1×1000C/20 1×1000P
NS 1000/20[c]	**500/20** 1×500/20 1×500P	**1000/20** 1×500/20 1×500/0	**1000/20** 1×500/20 1×500/0 1×500P	**1000/20** 1×1000/20 1×1000P
NS 2000/20[c]	**500/20** 1×500/20 1×500P	**1000/20** 1×500/20 1×500/0	**1500/20** 1×500/20 2×500/0	**2000/20** 1×1000/20 1×1000/0
	2 tabs/day	2 tabs/day	3 tabs/day	2 tabs/day

[a] Subjects in the simvastatin groups received niacin IR 50 mg to assist in maintaining the study blind.

[b] Subjects randomized to treatment with S40 received the same configuration of study medication as the S20 arm, with the following exceptions: 1 x 500P/20 instead of 1 x 500P from Weeks 1-8, 1 x 500P/20 and 1 x 500P instead of 2 x 500P from Weeks 9-12; and 1 x 1000P/20 instead of 1 x 1000P from Weeks 13-24.

[c] NS dosing is expressed in terms of niacin ER mg/simvastatin mg.

Dose Titration Regimen and Tablet Combinations – Dose Group B

Treatment	Treatment Phase (daily dose [mg], and tablet combination to achieve the dose)			
	Weeks 1-4	Weeks 5-8	Weeks 9-12	Weeks 13-24
S80[a]	**80** 1×500C/20 3×500P/20	**80** 1×500C/20 3×500P/20	**80** 1×500C/20 3×500P/20	**80** 1×1000C/20 3×1000P/20
NS 1000/40[b]	**500/40** 1×500/20 1×500P/20 2×500P	**1000/40** 2×500/20 2×500P	**1000/40** 2×500/20 2×500P	**1000/40** 1×1000/20 1×1000P/20 2×1000P
NS 2000/40[b]	500/40 1×500/20 1×500P/20 2×500P	1000/40 2×500/20 2×500P	1500/40 2×500/20 1×500/0 1×500P	2000/40 2×1000/20 2×1000P
	4 tabs/day	4 tabs/day	4 tabs/day	4 tabs/day

[a] Subjects in the simvastatin groups received niacin IR 50 mg to assist in maintaining the study blind.

[b] NS dosing is expressed in terms of niacin ER mg/ simvastatin mg.

Note: For a description of the tablets, refer to Table 4.

The dose titration regimen for each treatment arm is outlined in Table 5 for Dose Group A and in Table 6 for Dose Group B, together with the tablet combinations used to achieve each specific dose. Subjects were instructed to take the study medication by mouth once daily at bedtime with a low-fat snack. To help minimize flushing effects, at the Investigator's discretion, subjects were permitted to take aspirin, ibuprofen, or another non-steroidal anti-inflammatory drug (NSAID) approximately 30 minutes prior to study medication ingestion.

10.1.2.5 **Inclusion and Exclusion Criteria**

Inclusion Criteria:

1. Provide a written informed consent
2. Men or women 21 years of age or older.
3. Women of childbearing potential were to use contraception 3 months prior to Run-In Phase and to continue for the duration of the study.
4. A woman was not to be pregnant or breast-feeding, and not planning to become pregnant or to breast-feed during participation in this study
5. Patient had primary type II hyperlipidemia (i.e., patient did not have hyperlipidemia caused by an uncontrolled, underlying disease state such as hypothyroidism) or mixed dyslipidemia with non-HDL-C levels as specified in Table 1 or Table 2 below.
6. Patient taking anti-dyslipidemic medications other than simvastatin was willing to discontinue such medications for the duration of the study.
7. Non-HDL-C and LDL-C were considered elevated or at goal of they met or were below the NCEP Treatment Goals. (Changed from Treatment Options by Amendment #4)

Table 10.1.2.5-1

Risk Category[a]	Non-HDL-C (mg/dL) Level	LDL-C (mg/dL) Level
CHD or CHD risk equivalent	≥130 mg/dL	≥100 mg/dL
≥2 risk factors	≥160 mg/dL	≥130 mg/dL
0–1 risk factors	≥190 mg/dL	≥160 mg/dL

* Eligibility Based on NCEP-III Treatment Goals; these levels were considered elevated for study purposes, and values below these were considered at goal.

[a] Risk levels based on NCEP risk factors for developing CHD and Framingham 10-year risk scores.

NOTE: For subjects who were treatment-naïve under Amendment 4 at Screening, LDL-C was not to have exceeded 165 mg/dL, 215 mg/dL, and 249 mg/dL for each of the 3 risk categories, respectively.

Exclusion Criteria:

1. Subject had an allergy, hypersensitivity, or intolerance to niacin, statins, or their derivatives.
2. Subject consumed >2 alcoholic drinks per day or had a history of substance abuse or dependency within 12 months prior to Screening.
3. Subject had untreated or unsuccessfully treated psychiatric disease.