CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-078

STATISTICAL REVIEW(S)

2/11/08

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research
Office of Translational Sciences
Office of Biostatistics

STATISTICAL REVIEW AND EVALUATION

CLINICAL STUDIES

NDA/Serial Number:	022078/0
Drug Name:	Simcor (niacin extended-release and simvastatin) 500mg/20mg, 750mg/20mg, and 100mg/20mg tablets
Indication(s):	For primary hypercholesterolemia ~~—~~ mixed dyslipidemia and hypertriglyceridemia
Applicant:	Abbott
Date(s):	4/17/07; PDUFA date 2/17/08
Review Priority:	Standard
Biometrics Division:	Division of Biometrics 2 (DB2)
Statistical Reviewer:	Janice Derr, Ph.D.
Concurring Reviewers:	Jon T. Sahlroot, Deputy Division Director and Team Leader Thomas Permutt, Division Director
Medical Division:	Division of Metabolism and Endocrine Products (DMEP)
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Keywords: clinical studies, NDA review

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of gender by niacin interaction effects were not consistently less than 0.05, and the estimates were sensitive to the choice of imputation and analysis methods. In addition, the effect of gender was not as distinct for subjects taking niacin 1000 mg or 2000 mg combined with simvastatin 40 mg and compared to subjects taking simvastatin 80 mg. These findings support the applicant's summary that gender had some effect on certain endpoints but that this effect was not consistent.

Recommendations: This review (section 5.3) includes recommendations for the labeling text. There are no additional recommendations.

1.2 Brief Overview of Clinical Studies

Results from two clinical studies, "SEACOAST" and "OCEANS," are presented in this submission. SEACOAST was a randomized, double-blind, parallel arm study. OCEANS was an open-label, uncontrolled study with the primary objective of evaluating the long-term safety of NS 2000/40 (niacin 2000 mg / simvastatin 40 mg). The statistical review will cover the SEACOAST study. In both studies, the population consisted of men and women, 20 years of age or older, who met the specified diet, lipid and safety criteria for entry. The major inclusion criteria included primary type II hyperlipidemia or mixed dyslipidemia with specified criteria for elevated non-HDL and LDL.

In the SEACOAST study, subjects completed a run-in phase on either 20 mg or 40 mg simvastatin depending on their treatment history and LDL level. If subjects then met the entry criteria they were assigned to 1 of 2 dose groups according to the run-in simvastatin dose. Subjects taking 20 mg simvastatin were assigned to Dose Group A, and randomized to 1 of 3 treatment arms: niacin 1000mg / simvastatin 20 mg (NS 1000/20), niacin 2000mg / simvastatin 20 mg (NS 2000/20) and simvastatin 20 mg (S20). Subjects taking 40 mg simvastatin were assigned to Dose Group B and randomized to 1 of 3 treatment arms: niacin 1000mg / simvastatin 40 mg (NS 1000/40), niacin 2000mg / simvastatin 40 mg (NS 2000/40) and simvastatin 80 mg (S80). During the treatment phase, doses of NS were upwardly titrated at 4-week intervals until the maximum dose in a given treatment group had been achieved. Subjects then continued at the maximum dose for the remainder of the 24-week treatment period.

In the OCEANS study, subjects had a run-in phase on simvastatin 40 mg were randomized to one of two NS titration groups. These groups followed different upward titration schedules, consisting of three sets of changes, one upward change every four weeks for twelve weeks. The total duration of treatment on the maximum dose of NS 2000/40 was up to 52 weeks.

(3) the assumption that niacin-induced flushing is not related to the efficacy of the NS combination as measured by changes in non-HDL and key secondary lipid endpoints.

The smaller estimated effect sizes in the ANCOVA/LOCF model compared with the MMRM model did not affect important p-values to the extent of changing the statistical conclusions. However, it is important to note that smaller effect sizes have the potential to affect a superiority comparison differently from a non-inferiority comparison, and that both comparisons were used in the SEACOAST study.

I believe it is reasonable to report the estimated effect size from the applicant's preferred MMRM model in the label for Simcor, because the pattern of study dropouts are consistent with the model assumptions of the MMRM model that data was missing at random. However, I believe that these estimates should be presented along with the study results showing the percentage of subjects in each arm that did not complete the study. The estimates from the MMRM are most pertinent to subjects in the target population who are able to tolerate the NS combinations and can continue to take them over a long period of time.

2. INTRODUCTION

2.1 Overview

Dyslipidemia is considered a risk factor for coronary artery disease (CAD) and events such as myocardial infarction (MI) and cerebrovascular (CV) events. Dyslipidemia is often treated with HMG-CoA reductase inhibitors, or statins, which act to lower levels of LDL. Several large, prospective, randomized, controlled clinical trials have demonstrated an associated reduction in fatal and non-fatal CV events with the use of statins in high-risk populations. Overall, risk reductions have ranged from 20-42%. However, the results from these prevention trials also suggest the potential for further risk reduction. Abnormalities in HDL and TG are also risk factors for CAD, and these lipid components are not substantially affected by statins. This is the rationale for the use of combination therapies consisting of a statin and niacin, in order to target LDL, HDL and TG. Niacin and simvastatin have complementary mechanisms of action with differing relative impacts on atherogenic particles. Niacin acts to raise levels of HDL and to lower levels of TG, LDL and other ApoB-containing lipoproteins.[1]

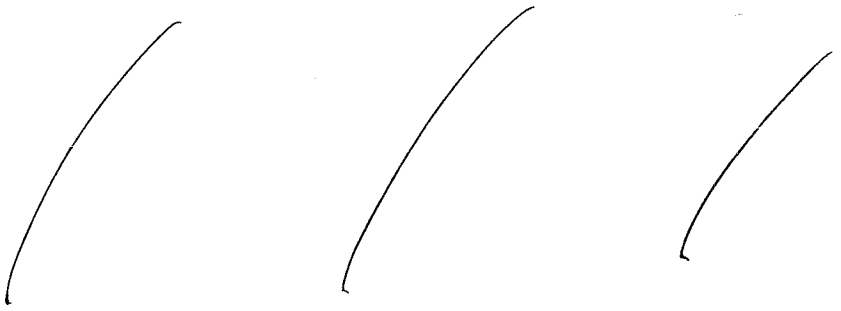
The applicant has developed a fixed-dose combination tablet containing niacin and simvastatin (NS) for the treatment of multiple lipid disorders. NS tablets consist of an extended-release niacin [redacted] with an immediate-release simvastatin. The niacin [redacted] is equivalent to Niaspan® (Kos). Simvastatin was approved in the US in 1991 (Zocor®, Merck & Co., Inc.). Niaspan was approved in the U.S. in 1997 as an antihyperlipidemic agent.[2]

[1] The source of this paragraph is Section 2.5 Clinical Overview, part 2.5.1.2 (paraphrased)
[2] The source of this paragraph is Section 2.5 Clinical Overview, part 2.5.1.1 (paraphrased)

The applicant is now seeking marketing approval for NS tablets with the following proposed indications[3]:

In patients with hypercholesterolemia requiring modifications of lipid profiles

- As an adjunct to diet to reduce elevated total cholesterol (Total-C), low-density lipoprotein cholesterol (LDL), non-high-density lipoprotein cholesterol (non-HDL), Apolipoprotein B (Apo B), triglycerides (TG), evels and to increase high-density lipoprotein cholesterol (HDL) in patients with primary hypercholesterolemia mixed dyslipidemia, and hypertriglyceridemia.



2.2 Scope of Statistical Review: Pivotal Efficacy and Safety Studies

The focus of this review is on the information hat is based on statistical findings from the Phase 3 study "SEACOAST." SEACOAST was a randomized, double-blind, parallel arm study. The design of SEACOAST is described in this section. A second Phase 3 study, "OCEANS," was an open-label, uncontrolled study with the primary objective of evaluating the long-term safety of NS 2000/40 (niacin 2000mg / simvastatin 40mg). The statistical review will not cover the OCEANS study. For additional information about this study, see the medical review.

2.2.1 Development of the SEACOAST Study Design

The Agency and the applicant discussed the development of the SEACOAST study over a period of several years, beginning with a pre-IND conference in 2002. I believe that an understanding of the discussion between the Agency and the applicant helps clarify the intended target population, the dose arms, the statistical comparisons used in the study and the number of subjects per arm. In my opinion, these aspects of the study design are important to understanding the conclusions about the efficacy of Simcor that can be supported by this study.

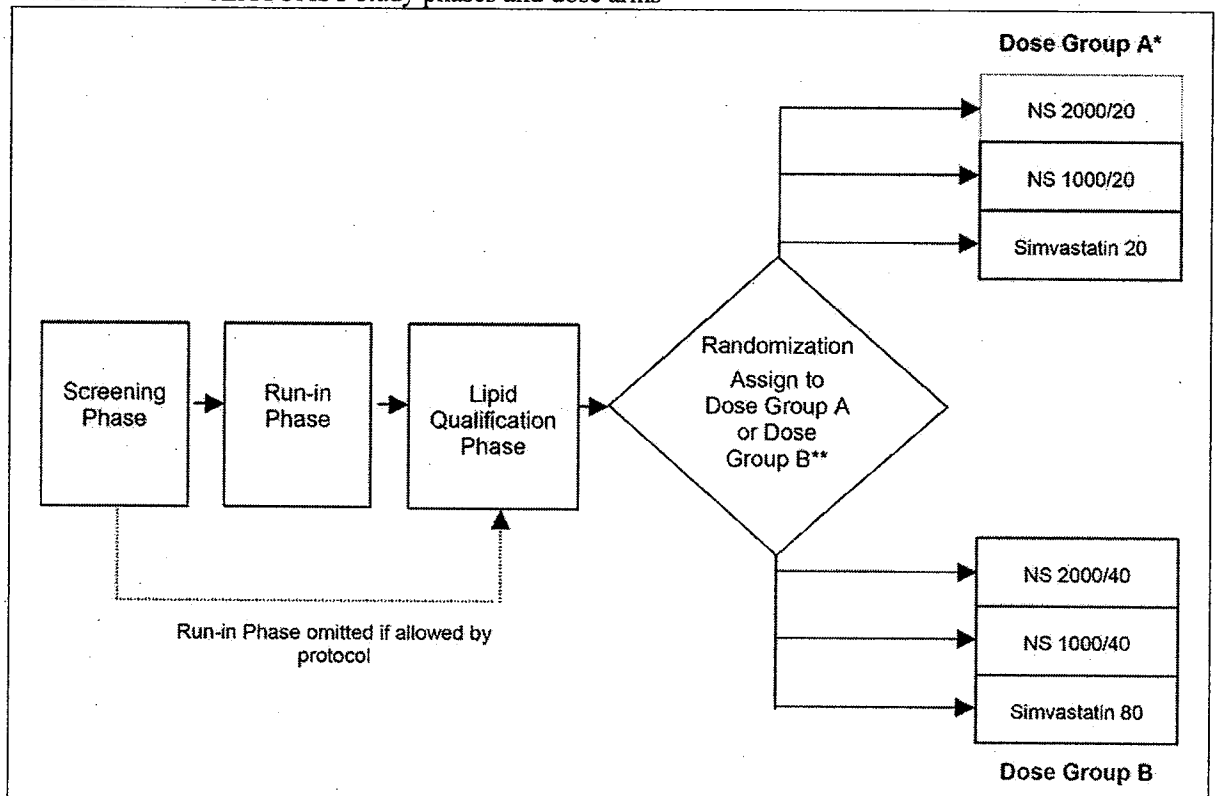
[3] The proposed indication is quoted from Section 2.5 Clinical Overview, part 2.5.1

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.[4] In response, the Agency requested an add-on study instead, with the intent to reflect the possible use of Simcor as add-on therapy, i.e., adding one or the other agent on when the LDL and/or non-HDL goals have not been met on single agent therapy. The Agency indicated that a study where the subjects 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. However, in my 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.

Target population: Two groups of subjects were defined by eligibility criteria for entry into SEACOAST. Simvastatin Low Dose Group A included subjects who were likely to reach acceptable levels of LDL with a lower daily dose of simvastatin, such as 20 mg. Simvastatin High Dose Group Group B included subjects who were likely to need a higher daily dose of simvastatin, such as 40 or 80mg. Eligibility was defined through an initial screening phase, an open-label simvastatin run-in phase and a lipid qualification phase (FIGURE 1). Key entry criteria are described in TABLE 1.

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

FIGURE 1 SEACOAST study phases and dose arms



** *[Comment from this reviewer: The text in the "Randomization" box is somewhat misleading. Subjects were separated by their medical histories into either Dose Group A or Dose Group B. They were then randomized into treatment arms within either Dose Group A or Dose Group B.]*

Source: SEACOAST Clinical Study Report, Figure 1

TABLE 1 SEACOAST non-HDL and LDL study lipid criteria

Risk Category*	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.

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.

Source: SEACOAST Clinical Study Report, Table 2

Simvastatin Low Dose Group A:

Dose Arms: Subjects who qualified for the low dose of simvastatin were randomized to 1 of 3 treatments:

- simvastatin 20mg (S20)
- niacin 1000mg/simvastatin 20mg (NS 1000/20)
- niacin 2000mg/simvastatin 20mg (NS 2000/20)

Statistical Comparisons: The dose arms in Dose Group A were designed for two superiority comparisons, arranged in a gate-keeper sequence. The first comparison was between NS 2000/20 and S20, and the second one between NS 1000/20 and S20 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.

I note that the protection of Type I error applies to the primary efficacy endpoint, non-HDL as a % of baseline from week 26. A statistically significant result for secondary efficacy endpoints, such as LDL and HDL, may support their inclusion in the indication for Simcor. However, in my opinion, actually including these secondary efficacy endpoints in the indication for Simcor is a clinical review issue.

Number of Subjects per Arm: The applicant estimated that NS 2000/20 and NS 1000/20 would lower non-HDL by an additional 14% and 6%, respectively, compared with S20. The applicant allocated 90 subjects to the S20 arm, 90 subjects to the NS 1000/20 arm and 45 subjects to the NS 2000/20 arm. With an estimated standard deviation of 14%, this allocation should provide > 99% power for the comparison between NS 2000/20 with S20 and 81% power for the comparison between NS 1000/20 and S20. Allowing for the 25% dropout rate, the total enrollment for Group A was targeted at 305 subjects. I confirmed these power calculations.

Simvastatin Low Dose Group B:

Dose Arms: Subjects who qualified for the high dose of simvastatin were randomized to 1 of 3 treatments:

- simvastatin 80 mg (S80)
- niacin 1000mg/simvastatin 40mg (NS 1000/40)
- niacin 2000mg/simvastatin 40mg (NS 2000/40)

The Agency and the applicant discussed the possible inclusion of a simvastatin 40 mg (S40) monotherapy arm in the high dose group, but this arm was not included. The Agency was concerned that the S40 monotherapy arm may not be appropriate for subjects in this dose group. This concern led the Agency to recommend a non-inferiority evaluation for the NS arms compared with the S80 arm, with a pre-defined margin of difference.[5]

[5] See a summary from The applicant of a (teleconference) meeting held on October 28, 2003, and the letter from the Agency to The applicant under IND 65187 dated March 16, 2004.

Statistical Comparisons: The treatment arms in Dose Group B were designed for a sequence of tests, using a gate-keeper sequence. The first test was a non-inferiority comparison of NS 2000/40 compared to S80. 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 NS 1000/40 compared to S80; and b) a superiority evaluation of NS 2000/40 compared to S80.

The Agency requested a pre-defined margin of difference for LDL, which was the primary efficacy endpoint in the early stages of development of the SEACOAST study.[6] The applicant proposed a margin of 6% for the percentage change between baseline and the study endpoint.[7] While the Agency did not respond explicitly to this proposal, the applicant noted in their minutes of the March 15, 2005 meeting that they assumed that the margin was acceptable based on the context of the discussion.

Choice of Non-Inferiority Margin of 6% for non-HDL as % Change from Baseline at Week 26. 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. When the applicant and the Agency agreed to change the primary efficacy endpoint from LDL to non-HDL, the non-inferiority margin of 6% was kept the same[8]. In my opinion, the 6% non-inferiority margin may be interpreted for non-HDL and LDL, but would not extend without additional justification to other lipid components such as HDL. In my opinion, this makes a non-inferiority evaluation unfeasible for these lipid components. I believe that the most unambiguous statistical support for the efficacy of Simcor in lipid components such as HDL and TG would come from a statistically significant comparison in the direction of superiority.

Number of Subjects per Arm: The applicant estimated that NS 2000/40 may lower non-HDL by 8% more than S80 (in the direction of superiority). With a non-inferiority margin of 6%, and a standard deviation of 14%, this comparison has > 99% power with 91 subjects in each of the NS 2000/40 arm and the S80 arm. The subsequent test of superiority between these two arms has 97% power. The applicant stated that allocating 70 subjects to the NS 1000/40 arm would provide approximately 80% power for the subsequent test of non-inferiority, without identifying the expected effect size for this comparison. I calculated that an expected effect size of 0 between the NS 1000/40 arm and the S80 arm results in 77% power for the non-inferiority comparison. Allowing for a 25% dropout rate, the enrollment in Group B was targeted at 335 subjects.

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[6] See letters from the Agency to The applicant under IND 65187 dated March 16, 2004 and March 27, 2004.
[7] See minutes from the March 14, 2005 meeting, in the letter from the Agency dated March 28, 2005.
[8] See minutes from the March 14, 2005 meeting, in the letter from the Agency dated March 28, 2005.

2.2.2. SEACOAST Study Schedule

During the double-blind treatment phase, doses of NS were upwardly titrated at 4-week intervals for up to 12 weeks until the maximum dose in a given treatment arm had been achieved (TABLE 2). Subjects then continued at the maximum dose for the remainder of the study. The total duration on blinded study medication for subjects who completed the study was 24 weeks. Subjects in the simvastatin monotherapy arms (S20 and S80) received 50 mg of niacin daily. The purpose of this addition was to maintain the overall study blind (by causing flushing or related symptoms in some subjects in the monotherapy arms) at a dose of niacin that was too low to have a therapeutic effect.

Efficacy was assessed based on fasting blood values measured at post-randomization weeks 4, 8, 12 and week 24 (or date of termination) for non-HDL, LDL, HDL, TG and other lipid endpoints (TABLE 2). Safety was evaluated based on data collected for AEs, flushing events, routine chemistry and hematology analyses, urinalysis, vital sign measurements, and physical examinations. Aspirin/flushing logs were used to document flushing events and aspirin or NSAID usage for flushing. Subjects were trained on how to complete the logs and were asked to complete them on a daily basis. The logs were collected and reviewed by the site personnel at every post-randomization visit.

TABLE 2 SEACOAST Study, titration and lipid assessment schedule

1. Titration schedule				
Dose Group A				
Simvastatin 20 mg [1]	S20			
Niacin 1000 mg / Simvastatin 20 mg	N500/S20	N1000/S20		
Niacin 2000 mg / Simvastatin 20 mg	N500/S20	N1000/S20	N1500/S20	N2000/S20
Dose Group B				
Simvastatin 80 mg [1]	S80			
Niacin 1000 mg / Simvastatin 40 mg	N500/S40	N1000/S40		
Niacin 2000 mg / Simvastatin 40 mg	N500/S40	N1000/S40	N1500/S40	N2000/S40
Week	1-4	5-8	9-12	13-24
2. Lipid assessment schedule				
Baseline	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**

[1] For purposes of maintaining the study blind, subjects in the simvastatin monotherapy arms (S20 and S80) received 50 mg of niacin

2.2.3 SEACOAST Study Sites

The SEACOAST study was conducted in 97 sites from 5 countries. A total of 662 subjects were randomized across 97 investigational sites (TABLE 3). There were 54 sites in the US, with a total of 286 subjects. The period of the study was from Mary 17, 2004 (first subject randomized) to September 25, 2996 (last subject completed).

TABLE 3 SEACOAST; Number of randomized subjects and sites by country

	SEACOAST	
Country	Number of sites	Number of subjects
US	54	286
Argentina	13	158
Colombia	7	73
Chile	4	8
Russia	19	137
Totals	**97**	**662**

Source: Analysis by this reviewer, database DM (randomized subjects)

2.3 Data Sources

The applicant submitted this NDA including the data to the FDA CDER Electronic Document Room (EDR). The submission is recorded in the EDR with the link shown in TABLE 4. The data sets were submitted in SAS v.5 transport format.

TABLE 4 Data sources for studies

Document: NDA 021989/SE1-001
CDER EDR link: \\CDSESUB1\N022078\000\
Company: Abbott
Drug: Simcor® tablets; Niaspan® (niacin extended-release) and simvastatin
Letter date: April 17, 2007

3. STATISTICAL EVALUATION

3.1 Evaluation of Efficacy

3.1.1. Implementation of the Study Protocol

Two events took place during the implementation of the study that affected the efficacy databases:

1. Problems with Russian study site RU02 that led the applicant to create two versions of each analysis database, one with and one without data from this site. The issue is described in the SEACOAST Clinical Study Report as follows:

> Following database lock, a not-for-cause audit of Russian study site RU02 uncovered occurrences of similar laboratory data for subjects who had clinic visits on the same day ... A computer program that applied objective criteria to determine similarities between laboratory values identified 10 pairs (total of 20 observations) of similar laboratory values encompassing data from 12 of the 20 subjects randomized at the site. The only suspect data from the study site RU02 were these objectively identified as being parts of similar pairs. While there were no significant issues with respect to the clinical conduct of the study and there was no other suspect data identified, it was decided that the primary dataset to be used for the efficacy analyses would be that obtained after removal of all data from all 20 subjects randomized at site RU02. Of note, Site RU02 enrolled subjects only into Dose Group A. Additionally, given the lack of evidence for suspect data beyond the identified similar pairs, a dataset defined by removing only the 10 suspect data pairs also was analyzed. The primary datasets to be used for safety analyses remained unchanged and included all subjects randomized at site RU02[9].

I reviewed the study results that the applicant presented for the primary and key secondary efficacy endpoints, both with and without site RU02 in the intention-to-treat and per-protocol databases. The results were not greatly changed in these two versions of each database (see summaries in part 3.1.6 of this review). For this reason, I chose to focus my review of disposition and efficacy on the ITT database that excluded site RU02.

2. The applicant discontinued recruitment into study arm S40, a simvastatin 40mg monotherapy arm in Dose Group B. After 5 subjects were randomized to this arm, a protocol amendment was implemented that discontinued this arm (with the concurrence of the Agency.) The modified intention-to-treat (mITT) database excludes efficacy data from study arm S40.

The safety database includes data from all subjects treated with study drugs, including data from Site RU02 and data from study arm S40.

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[9] SEACOAST Clinical Study Report, section 5.8.2 ("Changes in the Planned Analysis") with additional detail in Appendix 12.4

3.1.2. Disposition of Subjects in the SEACOAST Study

There were 662 subjects randomized in the study. In my analysis of disposition, I excluded the 5 subjects who were randomized to the S40 treatment arm before it was discontinued, and I excluded the 20 subjects who were enrolled at Russian study site RU02 (all in Dose Group A). My reason for doing this was to evaluate disposition in the subjects in the modified intention-to-treat (mITT) database that was used to analyze the primary and key secondary efficacy endpoints. With these exclusions, 616 subjects were randomized, 294 in Dose Group A (with 266 in the mITT database) and 343 in Dose Group B (with 322 in the mITT database; TABLE 5).

TABLE 5 Subject disposition

Dose Group A	**NS 1000/20**	**NS 2000/20**	**S20**	**Total**
Randomized	127	66	121	314
Exclude Site RU02[1]	-7	-6	-7	-20
	120	60	114	294
Excluded from mITT	-12	-4	-12	-28
Included in mITT	108	56	102	266
Completed study	82	43	93	218
Discontinued study: [2]	26	13	9	48
	(24.1%)	(23.2%)	(8.8%)	(18.0%)
Reason:				
Adverse event	12	8	4	24
Flushing [3]	*10*	*6*	*0*	*16*
Other AE	*2*	*2*	*4*	*8*
Withdrawal of consent	10	1	3	14
Protocol violation	2	3	2	7
Lost to follow-up	2	0	0	2
Other	0	1	0	1
Excluded from PP [4]	-22	-10	-8	-40
Included in PP	86	46	94	226
Dose Group B [5]	**NS 1000/40**	**NS 2000/40**	**S80**	**Total**
Randomized	118	102	123	343
Excluded from mITT	-7	-4	-10	-21
Included in mITT	111	98	113	322
Completed study	89	80	96	265
Discontinued study: [2]	22	18	17	57
	(19.8%)	(18.4%)	(15.0%)	(17.7%)
Reason:				
Adverse event	13	13	6	32
Flushing [3]	*7*	*8*	*1*	*16*
Other AE	*6*	*5*	*5*	*16*
Withdrawal of consent	5	3	5	13

Dose Group A	NS 1000/20	NS 2000/20	S20	Total
Protocol violation	1	1	2	4
Lost to follow-up	0	0	0	0
Other	3	1	4	8
Excluded from PP [4]	-20	-15	-17	-52
Included in PP	91	83	96	270

Notes:
[1] Site RU02 (Russia) was excluded because of data quality issues; 20 subjects had been randomized to Dose Group A, none to Dose Group B.
[2] The percentage of subjects who did not complete the study is based on the number in the mITT population
[3] "Flushing" or a related symptom such as pruritis or headache was listed as the primary reason for discontinuation in Listing 10.6.8 from the SEACOAST Clinical Study Report
[4] The number of subjects excluded from the Per Protocol (PP) population is based on the number in the mITT Population
[5] Dose Group B also included 5 subjects randomized to the S40 monotherapy arms; this arm was discontinued.
Source: Analysis by this reviewer

A larger percentage of subjects in the niacin-simvastatin arms dropped out before the study was concluded than in the simvastatin arms (TABLE 5, FIGURE 2B and FIGURE 3B). This difference may be largely due to niacin-induced flushing and related adverse events in the NS arms (TABLE 5). The overall percentage of study dropouts (17%), along with the differential in the percentage of dropouts between the NS and S arms, especially in Dose Group A, raised my concern about the statistical evaluation of the primary efficacy endpoints. For this reason, I evaluated the dynamics of dropping out due to flushing and related adverse events.

The attrition in the NS arms appears to have occurred at a steady rate throughout the 24-week period (FIGURE 2B and FIGURE 3B). The steady rate also appears to apply whether subjects withdrew early due to "flushing or related AE" or else due to "other reasons" (FIGURE 2A and FIGURE 3A). To arrive at this classification, I first evaluated the listing of subjects who discontinued because of an adverse event (AE). With input from Dr. Chowdhury, I classified these AEs as either "flushing or related AE," encompassing flushing as well as pruritis, headache and allergy, or "other AE." Then, I combined the cases that withdrew due to "other AE" with the cases that withdrew for other (non AE) reasons, such as "withdrawal of consent" or "protocol violation." This resulted in two categories of withdrawal, due to "flushing or related AE" or due to "other reasons." This characterization of subjects who discontinued early is provided in Appendix A. I recognize that the distinction between "flushing or related AE" and "other reason" is likely to be somewhat uncertain, not only because of the interpretation of the AE events, but also because some subjects who discontinued due to "withdrawal of consent" may have experienced symptoms of flushing as their primary reason for withdrawing their consent. These issues of interpretation may tend to make the disposition look similar between cases who withdrew early due to flushing or related AEs and those who withdrew early due to other reasons. However, in spite of these limitations I believe it was useful to evaluate the dynamics of disposition with respect to the adverse event of flushing.

At the protocol development stage, the Biometrics review team recommended using last observation carried forward (LOCF) as the primary method of imputation in the efficacy evaluation of the lipid endpoints. I believe that the disposition pattern in the study means that the LOCF imputation has a differential effect in the NS arms compared with the S arms. This differential effect would tend to reduce the apparent difference between the NS and the S arms. The reasoning behind this conclusion is as follows:

(1) The percentage of dropouts was greater in the NS arms than the S arms, so more subjects in the NS arms would have values imputed by LOCF than in the S arms.

(2) Subjects in the NS arms experienced a titration schedule of niacin. Through week 8, the schedule was the same for all NS arms, with 500 mg in weeks 1-4 and 1000 mg in weeks 5-8 (FIGURE 2C and FIGURE 3C). Subjects in the NS 2000/20 and NS 2000/40 arms did not receive the full dose of niacin until week 12. Subjects who discontinued prior to week 12 were not receiving the full dosage to which they had been assigned. The LOCF for these subjects is likely to represent a lower therapeutic effect than if they had completed the study.

(3) It may take up to 12 weeks for a subject to experience the full therapeutic effect of the NS combination product (based on a discussion with Dr. Chowdhury). For these reasons, subjects in the NS 2000/20 and NS 2000/40 arms may not express the full effect of their dosage until week 24. The LOCF for these subjects is likely to represent a lower therapeutic effect if they discontinued any time prior to week 24.

(4) There were no lipid measurements between week 12 and week 24 (FIGURE 2D and FIGURE 3D). A subject who dropped out after week 12 would not have a value for LOCF imputation that reflected his/her time on the full dosage of the NS arm to which he/she had been assigned.

The differential effect of LOCF imputation may have the net effect of reducing the apparent difference between the NS and S arms. For Dose Group A, where the NS combinations are evaluated by a superiority comparison to the S20 arm, this differential LOCF effect may result in a more conservative evaluation. This is less of a concern from a review perspective than the consequences for Dose Group B. In Dose Group B, where the NS combinations are evaluated by a non-inferiority comparison to the S80 arm, the differential LOCF effect may tend to support a non-inferiority conclusion when in fact the NS combination is inferior to the S80 arm. For this reason, I believe it is important to consider results from other analysis populations, such as the Per Protocol population, in the non-inferiority evaluation.

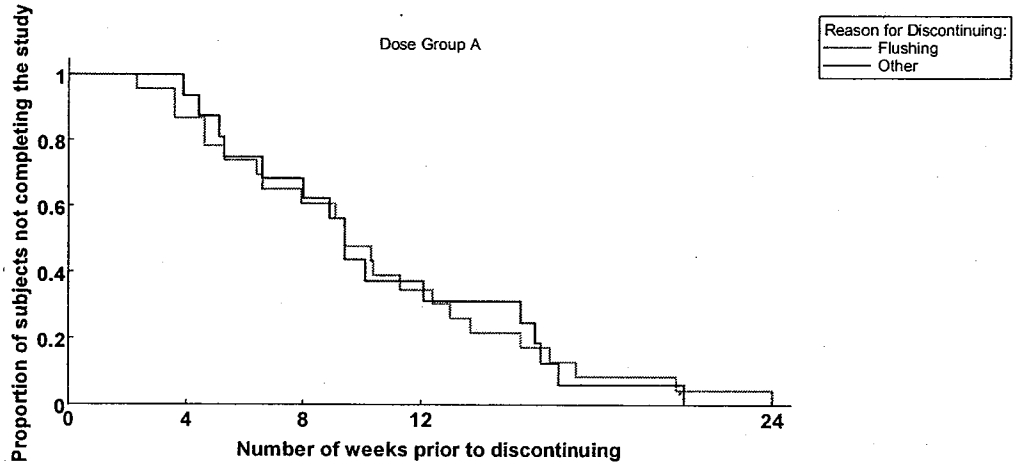
The applicant used an alternative method of handling missing data, which was to analyze the data with a statistical model that used the existing data only without imputation. The applicant maintained that this method was appropriate when subjects dropped out of the study and did not return (this characteristic is called "monotonic" in the missing data literature) and when the reasons for dropping out were not related to the primary endpoint ("missing at random" or

MAR). The Biometrics review team encouraged the applicant to present results from both methods, in order to compare results and to evaluate the applicant's proposed method further.

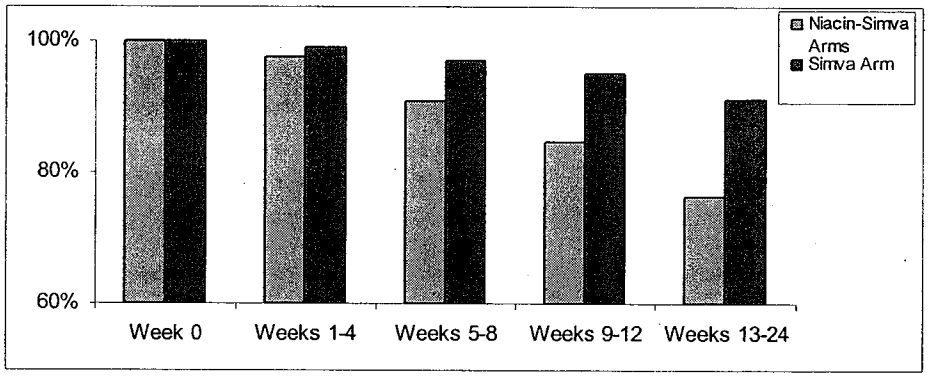
I believe that the assumptions of monotonicity and MAR are consistent with the disposition pattern in this study. The reason that a greater proportion of subjects dropped out in the NS arms than the S arms is related to adverse events associated with the niacin treatment. This is an issue of tolerance to niacin, and is not related to the levels of the primary or secondary lipid endpoints. For this reason, it may be reasonable to accept that the differential in missing values between the NS arms and the S arm is not likely to cause bias in estimating the efficacy of the NS product. However, I recommend that estimates from the MMRM model should be presented along with the percentage of dropouts in each study arm.

FIGURE 2 Disposition of subjects in Dose Group A, relative to niacin titration schedule and discontinuation due to flushing

A. Time course of disposition in subjects who did not complete the study, grouped by reason for discontinuing (either "flushing" or "other reason")



B. Proportion of randomized subjects remaining in the study at the end of each interval between lipid measurements, combined NS arms compared with the S20 arm



C. Niacin titration schedule

Dose Group A

Niacin 1000 mg / Simvastatin 20 mg	N500/S20	N1000/S20		
Niacin 2000 mg / Simvastatin 20 mg	N500/S20	N1000/S20	N1500/S20	N2000/S20
Week	1-4	5-8	9-12	13-24

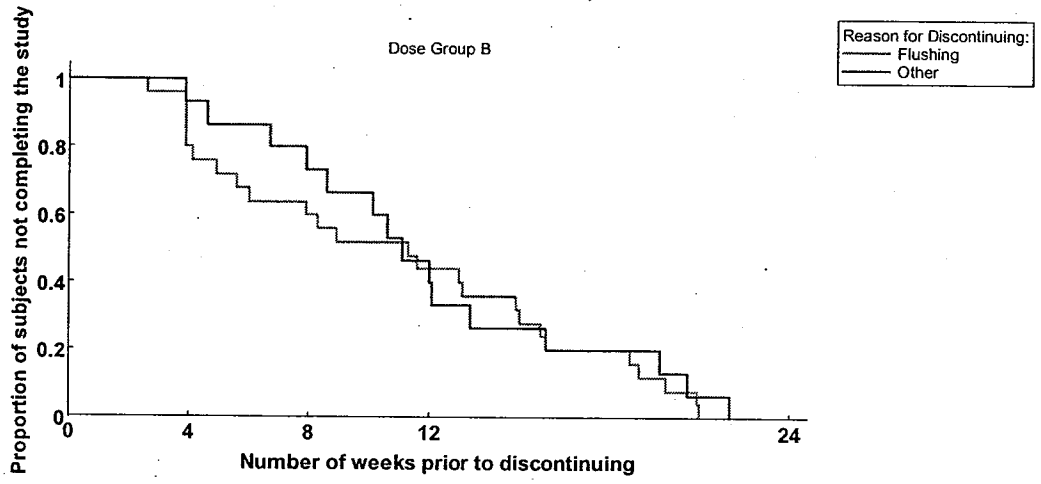
D. Lipid assessment schedule

Baseline	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**

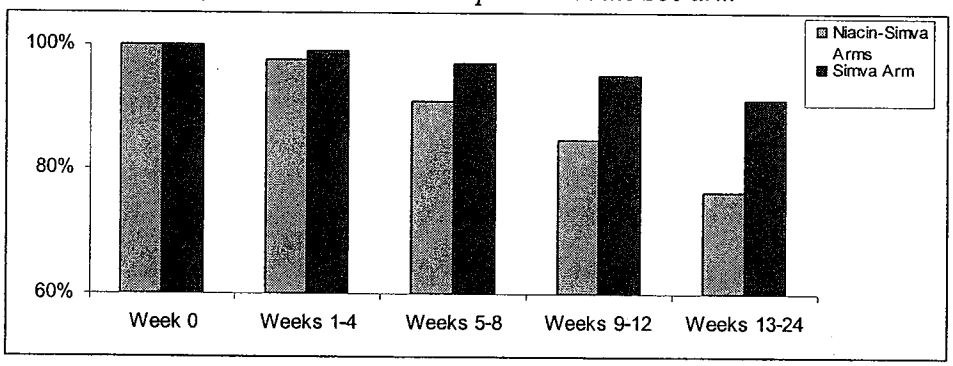
[1] For purposes of maintaining the study blind, subjects in the simvastatin monotherapy arms (S20 and S80) received 50 mg of niacin

FIGURE 3 Disposition of subjects in Dose Group B, relative to niacin titration schedule and discontinuation due to flushing

A. Time course of disposition in subjects who did not complete the study, grouped by reason for discontinuing (either "flushing" or "other reason")



B. Proportion of randomized subjects remaining in the study at the end of each interval between lipid measurements, combined NS arms compared with the S80 arm



C. Niacin titration schedule

Dose Group B

Niacin 1000 mg / Simvastatin 40 mg	N500/S40	N1000/S40		
Niacin 2000 mg / Simvastatin 40 mg	N500/S40	N1000/S40	N1500/S40	N2000/S40
Week	1-4	5-8	9-12	13-24

D. Lipid assessment schedule

Baseline	**Wk 4**	**Wk 8**	**Wk 12**	**Wk 24**

[1] For purposes of maintaining the study blind, subjects in the simvastatin monotherapy arms (S20 and S80) received 50 mg of niacin

3.1.3. Subject Demographic and Baseline Characteristics

Dose Groups A and B were relatively similar with respect to the distribution of subjects by sex (males comprised 51% of Dose Group A and 56% of Dose Group B), race/ethnicity group (75% of Dose Group A and 81% of Dose Group B were white), the average body mass index (mean BMI of 30 in both dose groups) and the percentage of non-smokers (79% in Dose Group A and 86% in Dose Group B; TABLE 6 and TABLE 8). A larger percentage of subjects were 65 years or older at baseline in Dose Group B (33%) than in Dose Group A (20%); more subjects in Group B had diabetes (38%) than in Group A (22%); and more subjects in Group B were in the "CHD and CHD risk equivalent" risk category (77%) than in Group A (57%; TABLE 6 and TABLE 8). These differences are consistent with the enrollment criteria for Dose Group B for subjects with a more advanced dyslipidemic condition than in Dose Group A.

In Dose Group A, median non-HDL (155.0-163.3 mg/dL) and LDL (112.8-119.0 mg/dL) levels were moderately elevated at baseline (TABLE 7). Median TG levels across the treatment arms (194.5-212.3 mg/dL) ranged from the upper end of the borderline high range to the high range. Median non-HDL values were more than 30 mg/dL higher than LDL values for each of the treatment arms, reflecting the contribution of relatively high TG levels. Median HDL levels were 42.5-43.0 mg/dL.

In Dose Group B, median non-HDL (130.5-143.0 mg/dL) and LDL (98.5-109.0 mg/dL) levels were only mildly elevated at baseline in Dose Group B (TABLE 9). Median TG levels across the treatment arms (140.5-155.5 mg/dL) ranged from the upper end of the normal range to the lower end of the borderline range. Median non-HDL values were approximately 30 mg/dL higher than LDL values for each of the treatment arms, consistent with a population with LDL elevation as the predominant lipid abnormality. Median HDL levels were 44.3-46.5 mg/dL.

Within each dose group, the dose arms were generally similar in terms of average baseline demographics, general characteristics and baseline lipid characteristics (TABLE 6 - TABLE 9).

TABLE 6 Demographic and baseline characteristics in Dose group A (314 randomized subjects)

Parameter	Statistic	S20 (N=121)	NS 1000/20 (N=127)	NS 2000/20 (N=66)	NS Group A Overall (N=193)
Age (years)	n	121	127	66	193
	mean (SD)	57.4 (10.2)	55.5 (10.4)	54.2 (10.5)	55.1 (10.4)
	median	58.0	56.0	55.0	56.0
	min, max	32.0, 76.0	30.0, 81.0	34.0, 75.0	30.0, 81.0
Age category					
<65 years	n (%)	87 (71.9)	100 (78.7)	54 (81.8)	154 (79.8)
≥65 years	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)
Race/ethnicity					
White	n (%)	91 (75.2)	95 (74.8)	50 (75.8)	145 (75.1)
Black	n (%)	1 (0.8)	1 (0.8)	0 (0.0)	1 (0.5)
Asian	n (%)	0 (0.0)	2 (1.6)	1 (1.5)	3 (1.6)
Hispanic	n (%)	29 (24.0)	27 (21.3)	13 (19.7)	40 (20.7)
Other	n (%)	0 (0.0)	2 (1.6)	2 (3.0)	4 (2.1)
BMI (kg/m^2)	n	121	127	65	192
	mean (SD)	29.3 (5.6)	29.0 (5.4)	31.4 (10.0)	29.8 (7.3)
	median	28.1	28.0	28.7	28.4
	min, max	19.3, 53.2	14.1, 53.0	19.2, 77.5	14.1, 77.5
Current smoker					
No	n (%)	100 (82.6)	98 (77.2)	55 (83.3)	153 (79.3)
Yes	n (%)	21 (17.4)	29 (22.8)	11 (16.7)	40 (20.7)
CHD Risk Category					
CHD and CHD risk equivalent	n (%)	70 (57.9)	74 (58.3)	36 (54.5)	110 (57.0)
≥2 risk factors	n (%)	42 (34.7)	36 (28.3)	20 (30.3)	56 (29.0)
0–1 risk factors	n (%)	9 (7.4)	17 (13.4)	10 (15.2)	27 (14.0)
Diabetes					
No	n (%)	98 (81.0)	101 (79.5)	49 (74.2)	150 (77.7)
Yes	n (%)	23 (19.0)	26 (20.5)	17 (25.8)	43 (22.3)
Lipid medication status at randomization					
Naïve	n (%)	13 (10.7)	20 (15.7)	16 (24.2)	36 (18.7)
Non-naïve	n (%)	108 (89.3)	107 (84.3)	50 (75.8)	157 (81.3)

* Excludes 5 subjects randomized to the S40 arm.

BMI=body mass index; n=number of subjects with available data; SD=standard deviation.

Source: SEACOAST Clinical Study Report, Table 12

TABLE 7 Baseline efficacy parameters from Dose Group A (314 randomized subjects)

Parameter	Statistic	S20 (N=121)	NS 1000/20 (N=127)	NS 2000/20 (N=66)	NS Group A Overall (N=193)
Non-HDL-C (mg/dL)	n	121	127	66	193
	mean (SD)	160.6 (29.9)	164.2 (27.0)	161.4 (30.2)	163.3 (28.1)
	median	155.0	163.5	156.3	162.0
	min, max	96.5, 270.0	103.5, 236.0	109.0, 249.0	103.5, 249.0
LDL-C (mg/dL)	n	121	127	66	193
	mean (SD)	118.9 (26.8)	121.6 (28.5)	117.6 (27.9)	120.2 (28.3)
	median	115.0	119.0	112.8	117.0
	min, max	51.0, 208.5	40.5, 200.0	63.0, 189.0	40.5, 200.0
HDL-C (mg/dL)	n	121	127	66	193
	mean (SD)	43.7 (10.4)	43.7 (10.9)	42.8 (9.3)	43.4 (10.3)
	median	43.0	42.5	42.8	42.5
	min, max	25.0, 91.0	25.0, 76.5	24.5, 64.5	24.5, 76.5
Total-C (mg/dL)	n	121	127	66	193
	mean (SD)	204.3 (30.9)	207.9 (28.9)	204.2 (29.9)	206.6 (29.2)
	Median	198.5	207.5	196.3	204.0
	min, max	130.5, 302.0	136.0, 284.5	144.5, 287.0	136.0, 287.0
TG (mg/dL)	n	121	127	66	193
	mean (SD)	206.0 (89.3)	217.4 (98.8)	215.8 (88.8)	216.8 (95.3)
	median	196.5	194.5	212.3	203.0
	min, max	60.0, 487.0	60.0, 539.5	66.5, 463.0	60.0, 539.5

Source: SEACOAST Clinical Study Report, Table 13

TABLE 8 Demographics and baseline characteristics of Dose Group B (343 randomized subjects)

Parameter	Statistic	S80 (N=123)	NS 1000/40 (N=118)	NS 2000/40 (N=102)	NS Group B Overall (N=220)
Age (years)	n	123	118	102	220
	mean (SD)	61.3 (10.6)	60.1 (10.8)	59.7 (8.5)	59.9 (9.8)
	median	60.0	62.0	59.0	60.0
	min, max	36.0, 88.0	32.0, 83.0	42.0, 82.0	32.0, 83.0
Age Category					
<65 years	n (%)	74 (60.2)	74 (62.7)	73 (71.6)	147 (66.8)
≥65 years	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)
Race/Ethnicity					
White	n (%)	96 (78.0)	92 (78.0)	87 (85.3)	179 (81.4)
Black	n (%)	11 (8.9)	13 (11.0)	5 (4.9)	18 (8.2)
Asian	n (%)	0 (0.0)	1 (0.8)	0 (0.0)	1 (0.5)
Hispanic	n (%)	15 (12.2)	12 (10.2)	10 (9.8)	22 (10.0)
Other	n (%)	1 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)
BMI (kg/m^2)	N	123	118	102	220
	mean (SD)	30.2 (6.2)	30.5 (5.7)	29.8 (4.7)	30.2 (5.3)
	median	28.6	29.4	29.4	29.4
	min, max	20.0, 47.7	20.8, 54.2	20.2, 44.9	20.2, 54.2
Current Smoker					
No	n (%)	103 (83.7)	102 (86.4)	86 (84.3)	188 (85.5)
Yes	n (%)	20 (16.3)	16 (13.6)	16 (15.7)	32 (14.5)
CHD Risk Category					
CHD and CHD risk equivalent	n (%)	94 (76.4)	92 (78.0)	77 (75.5)	169 (76.8)
≥2 risk factors	n (%)	27 (22.0)	23 (19.5)	22 (21.6)	45 (20.5)
0–1 risk factors	n (%)	2 (1.6)	3 (2.5)	3 (2.9)	6 (2.7)
Diabetes					
No	n (%)	81 (65.9)	71 (60.2)	66 (64.7)	137 (62.3)
Yes	n (%)	42 (34.1)	47 (39.8)	36 (35.3)	83 (37.7)

BMI=body mass index; n=number of subjects with available data; SD=standard deviation.

Source: SEACOAST Clinical Study Report, Table 14

TABLE 9 Baseline efficacy parameters of Dose Group B (343 randomized subjects)

Parameter	Statistic	S80 (N=123)	NS 1000/40 (N=118)	NS 2000/40 (N=102)	NS Group B Overall (N=220)
Non-HDL-C (mg/dL)	n	123	118	102	220
	mean (SD)	134.4 (28.3)	140.8 (30.5)	144.3 (29.8)	142.5 (30.1)
	median	130.5	135.5	143.0	138.3
	min, max	86.5, 299.0	96.5, 267.0	90.5, 224.0	90.5, 267.0
LDL-C (mg/dL)	n	123	118	102	220
	mean (SD)	102.7 (24.0)	109.4 (26.3)	110.7 (27.9)	110.0 (27.0)
	median	98.5	105.0	109.0	106.5
	min, max	56.5, 221.5	68.5, 227.0	47.0, 201.5	47.0, 227.0
HDL-C (mg/dL)	n	123	118	102	220
	mean (SD)	47.8 (10.8)	46.8 (10.6)	47.0 (9.4)	46.9 (10.1)
	median	46.5	44.3	46.3	45.0
	min, max	23.5, 86.0	29.0, 88.5	23.5, 86.0	23.5, 88.5
Total-C (mg/dL)	n	123	118	102	220
	mean (SD)	182.3 (30.4)	187.7 (32.8)	191.4 (31.8)	189.4 (32.3)
	median	178.0	180.0	187.8	183.3
	min, max	135.0, 352.5	133.5, 319.0	129.5, 280.0	129.5, 319.0
TG (mg/dL)	n	123	118	102	220
	mean (SD)	159.0 (72.9)	157.4 (62.3)	168.3 (69.1)	162.5 (65.6)
	median	140.5	147.3	155.5	148.8
	min, max	56.0, 515.5	51.5, 429.0	41.5, 408.5	41.5, 429.0

Source: SEACOAST Clinical Study Report, Table 15

3.1.4. Analysis Populations

Modified-Intention-to-Treat (mITT): The mITT population consists of all randomized subjects with a baseline measurement and at least one post-randomization measurement. Several versions of the mITT database were prepared, to accommodate the following considerations:

a) Data quality issues at Russian study site RU02: Because of concerns about data quality at site RU02, the applicant evaluated data from the mITT population both with and without data from this study site.

b) Methods of handling missing data from subjects who discontinued early: The applicant's preferred method of handling missing data was to analyze the non-missing data, with no imputation for missing data. The Agency recommended using last observation carried forward (LOCF) imputation. Because of this difference in preferred approaches, the applicant evaluated the mITT population both with and without the LOCF imputation.

Per-Protocol (PP): The PP population was a subset of the mITT. The PP included only subjects who completed the study and who met additional criteria based on protocol violations and specific compliance parameters that were finalized prior to unblinding the study.

Safety: The safety population included all subjects who could be reasonably assumed to have taken at least one dose of study drug.

3.1.5. Primary and Secondary Efficacy Endpoints

The primary efficacy endpoint in the SEACOAST study was percent change from baseline to week 24 in non-HDL. The secondary efficacy endpoints were percent change from baseline to week 24 in LDL, HDL, TC, TG and Lp(a). Of these, I selected LDL, HDL and TG for further review. I selected LDL because the atherogenic role of this endpoint is well characterized and because LDL has often been used as a primary endpoint in lipid-lowering drugs. I selected HDL and TG, not only for their importance in cardiovascular health but also because of the effect of niacin in raising HDL levels and lowering TG levels.

For non-HDL, LDL, HDL, TC, TG, TC:HDL ratio and LDL:HDL ratio, the protocol defined the baseline value as the mean of the values at the last two Qualification Visits. To calculate baseline for the TC:HDL and LDL:HDL ratios, the ratios were calculated for each Qualification Visit and then the average of the ratios from the last two Qualification Visits provided a baseline for these measurements. For all other efficacy parameters, baseline was defined as the last value before the first dose of randomized study drug.

3.1.6. Statistical Analysis Methods for Primary and Secondary Efficacy Endpoints

Primary Analysis Methods: The applicant and the Agency disagreed about the statistical analysis method (including the method for handling missing data from study dropouts) that would be considered primary. For this reason, the applicant agreed to present the results of both methods.

(1) Mixed model repeated measures with no imputation: The applicant preferred to use a mixed model repeated measures (MMRM) model with no imputation for missing data. The dependent variable was the percent change in non-HDL from baseline to week 24. Time was treated as a categorical variable, representing the four visits post-baseline (weeks 4, 8, 12 and 24). An unstructured variance-covariance matrix was used for the repeated measurement of time. Covariates in the mixed effects model were the subject's baseline non-HDL and the CHD risk factor. The CHD risk factor had three levels: "0-1 risk factors," "2+ risk factors" and "CHD and CHD risk equivalent." Factors in the model were the "pseudo-site" and the treatment arm. The "pseudo-site" factor represented a combination of data from small sites in similar geographic regions. The pooling scheme was designated prior to locking the database, based on a blinded review of the number of subjects per site.

(2) Analysis of covariance with LOCF imputation: The Biometrics review team recommended an analysis of covariance (ANCOVA) model with LOCF imputation for missing data. The dependent variable was the percent change in non-HDL from baseline to week 24. Covariates were the subject's baseline non-HDL and the CHD risk factor. Factors in the model were the "pseudo-site" and the treatment arm.

The statistical analysis plan also indicated that if an examination of model residuals suggested a markedly non-normal distribution of the residuals, then a non-parametric approach would be used to corroborate the inferential conclusions from the linear model. The applicant used the term "non-parametric" to refer to transforming the data into normal scores using the Blom method, and then applying the MMRM models to the transformed data. I will use this term in this review also, although in my opinion the term "robust" is more applicable. The applicant used this approach because the results of the Shapiro-Wilks test for normality of model residuals had p-values < 0.05 for all lipid endpoints. I evaluated the model residuals from the MMRM and ANCOVA models of non-HDL and LDL in order to gain a better understanding of the extent of departures from normality detected by the Sharpiro-Wilks test. In my opinion, this test is too sensitive and identifies departures from normality that are not problematic for inference and estimation in linear models.

The secondary efficacy endpoints were also analyzed by these two methods. For each secondary endpoint, the baseline covariate in the model referred to the baseline level of the dependent variable.

Evaluation of the Niacin-Simvastatin Combination Product: The niacin-simvastatin arms were compared to the simvastatin arm, using a different approach in each dose group. The overall type I error was protected within each dose group at an α of 0.05.

(1) Dose Group A: The primary objective for the SLD group (Dose Group A) was to evaluate superiority of each NS arm relative to the S20 arm with respect to percent lowering from baseline to week 24 of non-HDL. The secondary objectives for the SLD group were to evaluate superiority of NS relative to S20 with respect to percent lowering from baseline to week 24 of LDL, HDL, TC, TG and Lp(a).

To address the primary superiority for the SLD group, a step-down test was performed. First, the mean non-HDL percent change from baseline to week 24 of the S20 treatment 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. If the first test was significant, then the mean non-HDL endpoint of the S20 treatment 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. All tests were at the two-sided $\alpha = 0.05$ level.

(2) Dose Group B: The primary objective for the SHD group (Dose Group B) was to evaluate non-inferiority of each NS arm relative to the S80 arm with respect to percent lowering from baseline to week 24 of non-HDL. The secondary objectives for the SHD group were to evaluate non-inferiority of NS relative to S80 with respect to percent lowering from baseline to week 24 of LDL, HDL, TC, TG and LP(a).

To address the primary non-inferiority hypothesis for the SHD group, a step-down test was performed. First, a two-sided 95% CI for the mean difference in non-HDL endpoint between the S80 and NS 2000/40 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 less than or equal to 6%. If non-inferiority were concluded for NS 2000/40, then the non-inferiority of NS 1000/40 was evaluated in the same way. For any NS dose for which non-inferiority relative to S80 was concluded, superiority relative to S80 was tested at the two-sided $\alpha = 0.05$ level.

3.1.7. Results of the Statistical Analysis of Efficacy

Primary Efficacy Endpoint, non-HDL: In my opinion, the results from Dose Groups A and B support the efficacy of the NS combinations with respect to non-HDL.

Dose Group A:

- All three arms in Dose Group A resulted in an average lowering of non-HDL, expressed as a percentage change from baseline at week 24; -5.0% for S20, -13.6% for NS 1000/20 and -19.5% for NS 2000/20 (TABLE 10).

- The comparisons between the NS arms and the S20 arm were statistically significant for non-HDL. The statistical results support the interpretation that adding 1000 mg of niacin to simvastatin 20 mg produced an additional average lowering of non-HDL by 8.6% (TABLE 11, Result 1). Adding 2000 mg of niacin to simvastatin 20 mg produced an additional average lowering of non-HDL by 14.5%. The statistical results were consistent across all versions of the analysis data bases and statistical methodologies (TABLE 11). I confirmed these results for the mITT population, for both MMRM and ANCOVA models.

- The net effect of niacin in lowering non-HDL was somewhat less when estimated with LOCF imputation than when estimated without imputation (8.0% for LOCF and 8.6% for no imputation for NS 1000/20 vs. S20; and 12.0% for LOCF and 14.5% for no imputation with NS 2000/20 vs. S20; TABLE 11, Results 1 and 3). This difference is consistent with the interpretation that early dropouts in the NS arms may not have experienced the full therapeutic effect of their assigned dosage (see section 3.1.1). The net effect of niacin was higher when estimated from the PP population than with the mITT population for NS 1000/20 vs. S20 (9.3%), and similar for NS 2000/20 vs. S20 (14.3%; TABLE 11, Result 5). This finding is also consistent with the prediction that subjects who completed the study were more likely to express the full benefit of niacin than subjects who discontinued before week 24.

Dose Group B:

- All three arms in Dose Group B resulted in an average lowering of non-HDL at week 24 compared to baseline; -6.0% for S80, -6.7% for NS 1000/40 and -7.6% for NS 2000/40 (TABLE 12).

- The NS 2000/40 and NS 1000/40 arms were both non-inferior to the S80 arm with respect to average lowering of non-HDL (TABLE 13). This finding was consistent across both statistical analysis methods for the mITT database. I confirmed these results for the mITT population, for both MMRM and ANCOVA models. However, the non-inferiority

criterion was not met in the MMRM analysis of the PP database. The average net difference estimated from the PP database was somewhat larger in the direction of inferiority compared with the estimates from the mITT database.

Model Residuals: I evaluated the residuals from the MMRM analysis of non-HDL and LDL, because the applicant concluded that a non-parametric approach was needed to corroborate the results from the untransformed data analysis. Although the distribution of residuals had with some outlying values, the overall percentage of standardized residuals greater than 3.0 was 1.8% or less (FIGURE 4), and there were no standardized residuals < -3.0 in any of the analyses. I did not believe these outliers would be influential in the statistical analysis, even though they appear to skew the right tail of the distributions. This opinion is supported by the consistency of results between the non-transformed and the transformed data.

Choice of Estimates: Based on an evaluation of the analysis results and a consideration of the differential effect of dropout between the NS arms and the S arms, I recommend using the estimates from the MMRM model, using the mITT population without Study Site RU02, and with no imputation. However, the results should also include the percentage of subjects in each arm that did not complete the study.

TABLE 10 Percent change from baseline at week 24 in non-HDL for Dose Group A

	NS2000/S20		NS1000/S20		S20	
Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline (mg/dL)	56	163.1 (29.9)	108	164.8 (28.1)	102	163.7 (29.8)
Week 24 (mg/dL)	40	127.1 (45.6)	78	138.1 (40.6)	90	152.2 (40.7)
Change from baseline (%)	40	-20.9% (25.0)	78	-15.6% (24.8)	90	-7.1% (25.0)

Notes: mITT population without site RU02

Source: SEACOAST Clinical Study Report, Table 14.1.5A, 14.1.6A

TABLE 11 Results from the statistical analysis of non-HDL in Dose Group A

Group A, Non-HDL	**NS 2000/20 vs. S20**		**NS 1000/20 vs. S20**		
Analysis population Sites included Analysis method	Difference in means (95% CI)	p-value	Difference in means (95% CI)	p-value	Table Reference
1. mITT without LOCF omit site RU02 MMRM	-14.5 (-22.8, -6.3)	<0.001	-8.6 (-15.4, -1.9)	0.012	Table 14.1.1A
2. mITT without LOCF all sites MMRM	-14.2 (-22.2, -6.2)	<0.001	-8.5 (-15.1, -1.9)	0.011	Table 4.1.1A
3. mITT with LOCF omit site RU02 ANCOVA	-12.0 (-19.5, -4.4)	0.002	-8.0 (-14.3, -1.8)	0.012	Table 14.1.3A
4. mITT with LOCF all sites	-12.1 (-19.4, -4.9)	0.001	-7.9 (-14.0, -1.8)	0.011	Table 4.1.3A

Group A, Non-HDL	**NS 2000/20 vs. S20**		**NS 1000/20 vs. S20**		
ANCOVA					
5. PP omit site RU02 MMRM	-14.3 (-22.8, -5.9)	<0.001	-9.3 (-16.3, -2.4)	0.009	Table 14.1.4A
6. PP all sites MMRM	-14.0 (-22.3, -5.8)	<0.001	-8.8 (-15.6, -2.0)	0.012	Table 4.1.4A
	Difference in medians[1]		Difference in medians[1]		
7. mITT without LOCF omit site RU02 non-parametric MMRM	-15.2	<0.001	-6.5	0.007	Table 14.5.1A
8. mITT without LOCF all sites non-parametric MMRM	-15.1	<0.001	-6.4	0.006	Table 4.5.1A
9. mITT with LOCF omit site RU02 non-parametric ANCOVA	-11.0	<0.001	-8.6	0.007	Table 14.5.2A
10. mITT with LOCF all sites non-parametric ANCOVA	-11.1	<0.001	-8.7	0.006	Table 4.5.2A
11. PP omit site RU02 non-parametric MMRM	-14.3	<0.001	-5.8	0.006	Table 14.5.3A
12. PP all sites non-parametric MMRM	-13.2	<0.001	-6.5	0.008	Table 4.5.3A

[1] The sponsor did not report the 95% confidence interval for the comparisons from the non-parametric analyses.

TABLE 12 Percent change from baseline at week 24 in non-HDL for Dose Group B

	NS2000/S40		NS1000/S40		S80	
Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline (mg/dL)	98	144.4 (29.4)	111	141.2 (30.5)	113	134.5 (29.0)
Week 24 (mg/dL)	80	129.8 (47.3)	82	128.0 (35.8)	90	121.8 (26.7)
Change from baseline (%)	80	-10.6% (26.4)	82	-9.2% (18.5)	90	-8.0% (16.3)

Notes: mITT population

Source: SEACOAST Clinical Study Report, Table 4.1.13A, 4.1.14A

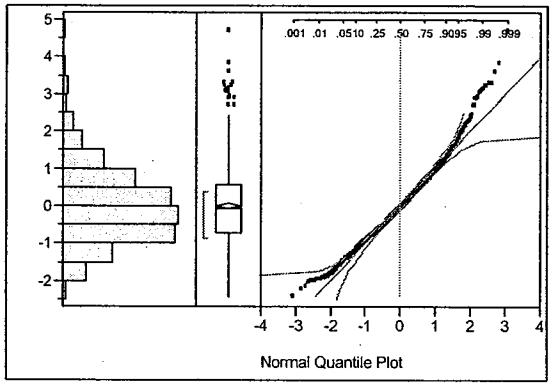
TABLE 13 Results from the statistical analysis of non-HDL in Dose Group B

Group B, non-HDL	**NS 2000/40 vs. S80**		**NS 1000/40 vs. S80**		
Analysis population Sites included Analysis method	Difference in means (95% CI)	NI criteria of 6.0% met? If yes, Superiority p-value	Difference in means (95% CI)	NI criteria of 6.0% met? If yes, Superiority p-value	Table Reference
1. mITT without LOCF all sites MMRM	-1.6 (-7.7, 4.5)	Yes 0.610	-0.7 (-6.6, 5.3)	Yes 0.826	Table 4.1.9A
2. mITT with LOCF all sites ANCOVA	-1.4 (-6.8, 4.1)	Yes 0.624	-0.1 (-5.4, 5.1)	Yes 0.968	Table 4.1.11A
3. PP all sites MMRM	1.0 (-5.0, 7.1)	No ---	2.3 (-3.7, 8.2)	No ---	Table 4.1.12A
	Difference in medians[1]		Difference in medians[1]		
4. mITT without LOCF all sites non-parametric MMRM	-7.0	Yes 0.666	-1.2	Yes 0.138	Table 4.5.4A
5. mITT with LOCF all sites non-parametric ANCOVA	-4.1	Yes 0.143	-1.6	Yes 0.678	Table 4.5.5A
6. PP all sites non-parametric MMRM	-4.1	Yes 0.403	-0.7	No ---	Table 4.5.6A

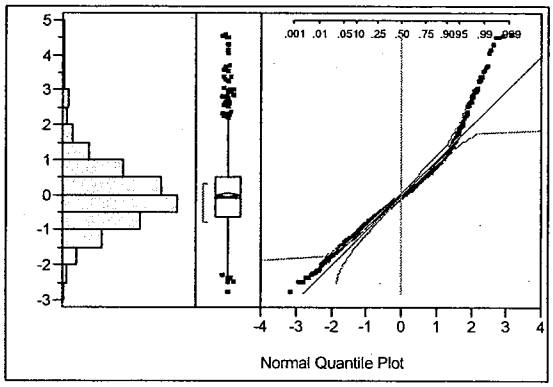
[1] The sponsor did not report the 95% confidence interval for the comparisons from the non-parametric analyses, so the determination of non-inferiority was not confirmed.

FIGURE 4 Distribution of standardized residuals from MMRM analysis of non-HDL and LDL

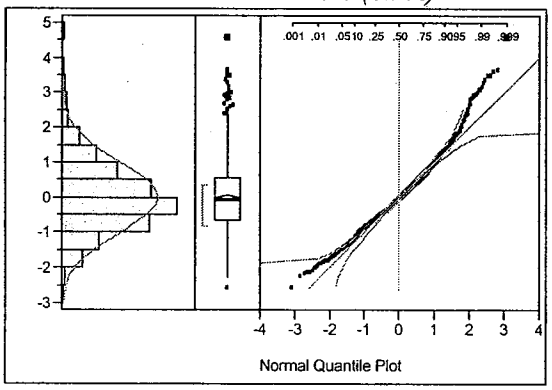
Group A: Non-HDL.
11 standardized residuals > 3.0 (1.0%)



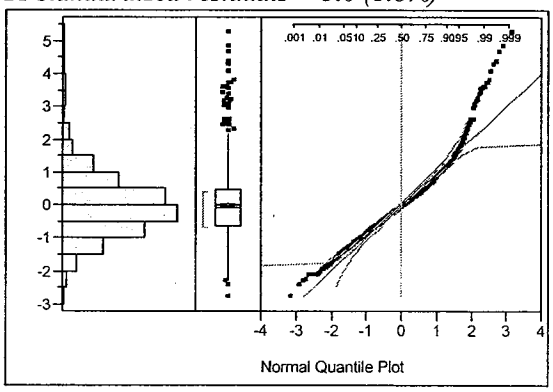
Group B: Non-HDL
16 standardized residuals > 3.0 (1.4%)



Group A: LDL
10 standardized residuals > 3.0 (0.9%)



Group B: LDL
21 standardized residuals > 3.0 (1.8%)



Notes: 1150 data points (322 subjects in the mITT database and up to four measurement periods)
There were no standardized residuals < -3.0

Source: Analysis by this reviewer

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LDL: In my opinion, the statistical test results from Dose Groups A and B do not support conclusions about the efficacy of the NS combinations with respect to LDL. While the average LDL is lowered more in the NS 1000/20 and 2000/20 arms compared with S20 in Dose Group A, the differences are not statistically significant. The difference between LDL lowering in the NS 1000/40 and NS 2000/40 arms compared with the S80 arm in Dose Group B does not meet the criteria for non-inferiority; in fact, these statistical comparisons are significant in the direction of inferiority.

Dose Group A:

- All three arms in Dose Group A resulted in an average lowering of LDL, expressed as a percentage change from baseline at week 24; -6.7% for S20, -11.9% for NS 1000/20 and -14.3% for NS 2000/20 (TABLE 14).

- The average LDL was not significantly different between the NS 2000/20 arm and the S20 arm, expressed as a percentage change from baseline at week 24 (TABLE 15). The non-significant comparison for NS 2000/20 vs. S20 means that the NS 1000/20 vs. S20 comparison should not be evaluated. However, the p-value of this comparison is given in TABLE 15 for descriptive purposes; none of the p-values for the NS 1000/20 vs. S20 comparisons are less than 0.05. I confirmed these results for the mITT population, for both MMRM and ANCOVA models. These results were consistent across different versions of the analysis data bases and statistical methodologies.

- The results of the statistical tests do not support the efficacy of adding either 2000 mg or 1000 mg of niacin to simvastatin 20 mg with respect to LDL.

Dose Group B:

- All three arms in Dose Group B resulted in an average lowering of LDL; -11.4% for S80, -7.1% for NS 1000/20 and -5.1% for NS 2000/20 (TABLE 16).

- The NS 2000/40 arm did not meet the criterion for non-inferiority in comparison to the S80 arm. In fact, the S80 arm appears to have a superior level of LDL lowering compared with the NS 2000/40 arm. The 95% confidence interval of this comparison does not include 0 in the direction of superiority of the S80 arm (TABLE 17; mITT population). However, the study protocol did not pre-specify a superiority evaluation in this direction. In the event that the NS 2000/40 arm was not non-inferior to the S80 arm, the protocol specified that further testing would not take place. The result of evaluating the NS 1000/40 arm for non-inferiority compared to the S80 arm is given in TABLE 17 for descriptive purposes only. These comparisons also do not meet the criterion for non-inferiority.

TABLE 14 Percent change from baseline at week 24 in LDL for Dose Group A

	NS2000/S20		NS1000/S20		S20	
Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline (mg/dL)	56	118.0 (29.1)	108	121.0 (29.4)	102	119.8 (27.3)
Week 24 (mg/dL)	40	99.1 (37.0)	78	105.9 (40.6)	90	112.5 (34.1)
Change from baseline (%)	40	-14.3% (28.8)	78	-11.9% (30.7)	90	-6.7% (25.2)

Notes: mITT population without site RU02

Source: SEACOAST Clinical Study Report, Tables 14.2.4A, 14.2.5A

TABLE 15 Results from the statistical analysis of LDL in Dose Group A

Group A, LDL	**NS 2000/20 vs. S20**		**NS 1000/20 vs. S20**		
Analysis population Sites included Analysis method	Difference in means (95% CI)	p-value[1]	Difference in means (95% CI)	p-value[1]	Table Reference
1. mITT without LOCF omit site RU02 MMRM	-8.1 (-17.6, 1.4)	0.095	-5.4 (-13.2, 2.4)	0.173	Table 14.2.1A
2. mITT with LOCF omit site RU02 ANCOVA	-5.9 (-14.6, 2.8)	0.185	-5.8 (-13.0, 1.5)	0.117	Table 14.2.2A
3. PP omit site RU02 MMRM	-7.4 (-17.0, 2.3)	0.134	-6.6 (-14.6, 1.3)	0.102	Table 14.2.3A
	Difference in medians[2]		Difference in medians[2]		
4. mITT without LOCF omit site RU02 non-parametric MMRM	-7.1	0.063	-6.0	0.086	Table 14.5.4A
5. mITT with LOCF omit site RU02 non-parametric ANCOVA	-6.0	0.110	-6.8	0.053	Table 14.5.5A
6. PP omit site RU02 non-parametric MMRM	-6.1	0.089	-5.0	0.064	Table 14.5.6A

[1] A p-value > 0.05 in the N2000/20 vs. S20 comparison results in stopping the sequence of comparisons. In this situation, the p-value for the comparison of NS 1000/20 vs. S20 is presented for descriptive purposes only.

[2] The applicant did not report the 95% confidence interval for the comparisons from the non-parametric analyses.

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TABLE 16 Percent change from baseline at week 24 in LDL for Dose Group B

	NS2000/S40		NS1000/S40		S80	
Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline (mg/dL)	98	111.2 (27.1)	111	110.3 (26.5)	113	103.0 (24.6)
Week 24 (mg/dL)	80	105.1 (39.7)	82	102.6 (31.4)	90	90.8 (25.0)
Change from baseline (%)	80	-5.1% (27.5)	82	-7.1% (20.5)	90	-11.4% (18.9)

Notes: mITT population

Source: SEACOAST Clinical Study Report, Tables 4.2.11A, 4.2.12A

TABLE 17 Results from the statistical analysis of LDL in Dose Group B

Group B, LDL Analysis population Sites included Analysis method	**NS 2000/40 vs S80** Difference in means (95% CI)	NI criteria of 6.0% met? If yes, Superiority p-value	**NS 1000/40 vs. S80** Difference in means (95% CI)	NI criteria of 6.0% met? If yes, Superiority p-value	Table Reference
1. mITT without LOCF all sites MMRM	6.7 (0.1, 13.4)[1]	No ---	4.8 (-1.8, 11.4)[2]	No ---	Table 4.2.8A
2. mITT with LOCF all sites ANCOVA	6.1 (0.2, 12.1)[1]	No ---	4.7 (-1.1, 10.5)[2]	No ---	Table 4.2.9A
3. PP all sites MMRM	8.6 (2.0, 15.2)[1]	No ---	7.0 (0.4, 13.5)[2]	No ---	Table 4.2.10A
	Difference in medians[3]		Difference in medians[3]		
4. mITT without LOCF all sites non-parametric MMRM	1.1	No ---	4.1	No ---	Table 4.5.10A
5. mITT with LOCF all sites non-parametric ANCOVA	2.0	No ---	2.9	No ---	Table 4.5.11A
6. PP all sites non-parametric MMRM	3.4	No ---	4.8	No ---	Table 4.5.12A

[1] The S80 arm may be superior to the NS 2000/40 arm in the LDL endpoint, although this evaluation step was not included in the analysis plan.

[2] When non-inferiority is not supported in the NS 2000/40 arm, the NS 1000/40 arm should not be evaluated for non-inferiority. In this situation, the results of the non-inferiority evaluation of NS 1000/40 vs. S80 are presented in this table for descriptive purposes only.

[3] The applicant did not report the 95% confidence interval for the comparisons from the non-parametric analyses, so the determination of non-inferiority was not confirmed.

HDL: In my opinion, the results from Dose Groups A and B support the efficacy of the NS combinations with respect to HDL.

Dose Group A:

- All three arms in Dose Group A resulted in an average increase of HDL, expressed as a percentage change from baseline at week 24; 7.8% for S20, 20.7% for NS 1000/20 and 29.0% for NS 2000/20 (TABLE 18).

- The comparisons between the NS arms and the S20 arm were statistically significant (TABLE 20, Result 1). The statistical results support the interpretation that adding 1000 mg of niacin to simvastatin produced an additional average increase of HDL by 12.5%. Adding 2000 mg of niacin to simvastatin 20 mg produced an additional average increase of HDL by 21.2% (TABLE 20, Result 1).

- The net effect of niacin was somewhat lower when estimated with LOCF imputation than when estimated without imputation (TABLE 20, Results 1 and 2). This finding is consistent with the results for non-HDL.

Dose Group B:

- The S80 arm had little change in average HDL at week 24 compared to baseline (0.1%). Both NS arms resulted in an average increase of HDL at week 24; 15.4% for NS 1000/20 and 24.4% for NS 2000/20 (TABLE 19).

- Both the NS 2000/40 and NS 1000/40 arms were significantly superior to the S80 arm with respect to average increase of HDL, with p-values < 0.001 (TABLE 20). This finding was consistent across the statistical analysis methods for the mITT and PP databases. For this reason I believe that these results support the efficacy of the NS arms with respect to HDL.

TABLE 18 Percent change from baseline at week 24 in HDL for Dose Group A

	NS2000/S20		NS1000/S20		S20	
Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline (mg/dL)	56	42.4 (9.8)	108	43.3 (11.0)	102	43.2 (9.4)
Week 24 (mg/dL)	40	53.9 (14.1)	78	51.2 (13.8)	90	45.9 (11.0)
Change from baseline (%)	40	29.0% (27.6)	78	20.7% (18.5)	90	7.8% (15.6)

Notes: mITT population without site RU02

Source: SEACOAST Clinical Study Report, Tables 14.2.11A, 14.2.12A

TABLE 19 Percent change from baseline at week 24 in HDL for Dose Group B

	NS2000/S40		NS1000/S40		S80	
Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline (mg/dL)	98	47.2 (9.5)	111	47.0 (10.7)	113	47.9 (10.8)
Week 24 (mg/dL)	80	58.9 (14.2)	82	53.9 (13.8)	90	47.8 (12.3)
Change from baseline (%)	80	24.4% (19.9)	82	15.4% (15.5)	90	0.1% (13.0)

Notes: mITT population

Source: SEACOAST Clinical Study Report, Tables 4.2.23A, 4.2.24A

TABLE 20 Results from the statistical analysis of HDL in Dose Groups A and B

Group A, HDL	**NS 2000/20 vs S20**		**NS 1000/20 vs. S20**		
Analysis population Sites included Analysis method	Difference in means (95% CI)	p-value	Difference in means (95% CI)	p-value	Table Reference
1. mITT without LOCF omit site RU02 MMRM	21.2 (14.4, 28.1)	<0.001	12.5 (6.9, 18.1)	<0.001	Table 14.2.8A
2. mITT with LOCF omit site RU02 ANCOVA	16.6 (10.5, 22.7)	<0.001	10.8 (5.8, 15.9)	<0.001	Table 14.2.9A
3. PP omit site RU02 MMRM	21.0 (14.0, 28.0)	<0.001	12.1 (6.3, 17.8)	<0.001	Table 14.2.10A
Group B, HDL	**NS 2000/40 vs S80**		**NS 1000/40 vs. S80**		
Analysis population Sites included Analysis method	Difference in means (95% CI)	P-value[1]	Difference in means (95% CI)	P-value[1]	Table Refer-ence
4. mITT without LOCF all sites MMRM	23.7 (18.9, 28.5)	<0.001	16.0 (11.2, 20.7)	<0.001	Table 4.2.20A
5. mITT with LOCF all sites ANCOVA	22.4 (18.1, 26.6)	<0.001	15.2 (11.1, 19.4))	<0.001	Table 4.2.21A
6. PP all sites MMRM	24.0 (19.1, 29.0)	<0.001	15.1 (10.2, 20.0)	<0.001	Table 4.2.22A

[1] A p-value < 0.05 supports the conclusions that the NS 2000/40 arm is superior to S80 in the HDL endpoint. However, the analysis plan was not entirely appropriate for this secondary endpoint because a non-inferiority margin for HDL was not pre-specified.

TG: The average TG was lower in the NS 2000/20 arm and the NS 1000/20 arm compared to the S20 arm at week 24, expressed as a percentage change from baseline. The comparisons between the NS arms and the S20 arm were statistically significant (TABLE 23).

Both the NS 2000/40 and NS 1000/40 arms were significantly superior to the S80 arm with respect to average lowering of TG with p-values < 0.001. For this reason, I believe that these results support the efficacy of the NS arms with respect to TG.

TABLE 21 Percent change from baseline at week 24 in TG for Dose Group A

	NS2000/S20		NS1000/S20		S20	
Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline (mg/dL)	56	225.0 (86.5) median 214.3	108	222.9 (97.4) median 209.5	102	216.2 (89.8) median 208.5
Week 24 (mg/dL)	40	140.1 (89.5) median 114.0	79	164.2 (97.8) median 143.0	90	201.7 (132.3) median 162.0
Change from baseline (%)	40	-31.8% (37.3) median -38.0%	79	-23.2% (31.2) median -26.5%	90	-4.0% (44.2) median -15.3%

Notes: mITT population without site RU02

Source: SEACOAST Clinical Study Report, Tables 14.2.25A, 14.2.26A

TABLE 22 Percent change from baseline at week 24 in TG for Dose Group B

	NS2000/S40		NS1000/S40		S80	
Timepoint	N	Mean (SD)	N	Mean (SD)	N	Mean (SD)
Baseline (mg/dL)	98	166.7 (69.9) median 149.5	111	155.0 (57.4) median 144.5	113	158.4 (72.7) median 140.5
Week 24 (mg/dL)	80	122.7 (81.1) median 103.0	83	128.2 (63.7) median 110.0	91	155.0 (65.3) median 145.0
Change from baseline (%)	80	-24.8% (40.8) median -31.8%	83	-34.0% median -22.8%	91	4.8% (29.1) median 0.3%

Notes: mITT population

Source: SEACOAST Clinical Study Report, Tables 4.2.47A, 4.2.48A

TABLE 23 Results from the statistical analysis of TG in Dose Groups A and B

Group A, TG	**NS 2000/20 vs S20**		**NS 1000/20 vs. S20**		
Analysis population Sites included Analysis method	Difference in means (95% CI)	p-value	Difference in means (95% CI)	p-value	Table Reference
1. mITT without LOCF omit site RU02 MMRM	-26.9 (-40.6, -13.2)	<0.001	-18.7 (-29.9, -7.5)	<0.001	Table 14.2.22A
2. mITT with LOCF omit site RU02 ANCOVA	-23.1 (-36.3, -10.0)	<0.001	-14.9 (-25.9, -4.0)	0.007	Table 14.2.23A
3. PP omit site RU02 MMRM	-27.6 (-41.3, -14.0)	<0.001	-18.6 (-29.8, -7.4)	<0.001	Table 14.2.24A
Group B, TG	**NS 2000/40 vs S80**		**NS 1000/40 vs. S80**		
Analysis population Sites included Analysis method	Difference in means (95% CI)	P-value[1]	Difference in means (95% CI)	P-value[1]	Table Reference
4. mITT without LOCF all sites MMRM	-27.1 (-37.1, -17.0)	<0.001	-19.1 (-28.9, -9.2)	<0.001	Table 4.2.44A
5. mITT with LOCF all sites ANCOVA	-25.5 (-34.0, -16.9)	<0.001	-17.6 (-25.9, -9.4)	<0.001	Table 4.2.45A
6. PP all sites MMRM	-23.0 (-33.1, -12.9)	<0.001	-16.5 (-26.4, -6.6)	<0.001	Table 4.2.46A

[1] A p-value < 0.05 supports the conclusions that the NS 2000/40 arm is superior to S80 in the TG endpoint. However, the analysis plan was not entirely appropriate for this secondary endpoint because a non-inferiority margin for HDL was not pre-specified.

3.2 Evaluation of Safety

An evaluation of safety is primarily covered in the FDA clinical review by Dr. Iffat Chowdhury.

4. FINDINGS IN SPECIAL/SUBGROUP POPULATIONS

4.1 Gender, Race and Age

Most subjects in the SEACOAST study were Caucasian (75.1%; TABLE 6). The number of subjects in the non-Caucasian categories was small, thus not allowing a reliable conclusion on potential race-related differences in the effect of the NS combinations on non-HDL and other lipid components. The applicant did not provide summary tables for gender and age group in the clinical report, but provided links to the summary output from analyses of these subgroups. The applicant's conclusion was that age group (with a cut point of 65 years) did not appear to make a difference in the effect of the NS combinations, and that gender had some effect on certain endpoints but that this effect was not consistent. For this reason, the applicant did not include separate summary tables by gender in the draft label.

After evaluating the summary tables for age group, I agree with the applicant's conclusion that age group did not make a difference in the effect of the NS combinations. However, I believe that the effect of gender was similar to the effect previously reported for niacin,

With respect to the statistical exploration of the gender effect, I used the following two approaches:

(1) I estimated the mean and 95% confidence interval of the two comparisons between the NS and S arms for each sex, for Dose Groups A and B, using the MMRM method and the ANCOVA/LOCF method.

(2) I evaluated the interaction of gender with each comparison between NS and S arms by constructing two linear contrasts. For Dose Group A, the two contrasts were "males(NS1000/20-S20) – females(NS1000/20-S20)" and "males(NS2000/20-S20) – females(NS2000/20-S20)." For Dose Group B, the two contrasts were "males(NS1000/40–S80) – females(NS1000/40–S80)" and "males(NS2000/40–S80) – females(NS2000/40–S80)." For the ANCOVA/LOCF model, these contrasts were from the means defined by the ARM by SEX interaction. For the MMRM model, these contrasts were from the means defined by the VISITDATE by ARM by SEX interaction.

Females in Dose Group A who took the NS combinations experienced more lowering of non-HDL and LDL, on average, than males (TABLE 24). However, the estimates were sensitive to the analysis method. This sensitivity reflects the greater proportion of study dropouts among females compared with males in Dose Group A. In the NS2000/20 arm, 10/24 (42%) of randomized females did not complete the study, leaving only 14 at week 24 (TABLE 24). Because the LOCF imputation tends to reflect less non-HDL and LDL lowering in subjects who did not complete the study, the difference in response between males and females is less when estimated from the ANCOVA/LOCF model than when estimated from the MMRM model. The interaction with gender had a p-value less than 0.05 only for the comparison between NS1000/20 vs. S20, with the MMRM model (the p-value was 0.056 for the ANCOVA/LOCF analysis of this interaction; (TABLE 24)).

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 NS arms and the S80 arms was also not as marked (TABLE 25). These findings support the applicant's summary that gender had some effect on certain endpoints but that this effect was not consistent.

TABLE 24 Results from the statistical analysis of gender in Dose Group A

		NS 2000/20 vs. S20		**NS 1000/20 vs. S20**		
	Method[1]	Difference in means (95% CI)	p-value[2]	Difference in means (95% CI)[2]	p-value	Table Reference
Non-HDL	MMRM		0.953		0.042	
	LOCF		0.199		0.056	
Males	MMRM	-7.0 (-17.6, 3.7)		-4.4 (-13.9, 5.0)		14.4.1A
	LOCF	-6.8 (-18.0, 4.9)		-1.8 (-10.9, 7.2)		
Females	MMRM	-26.2 (-39.0, -13.3)		-13.4 (-22.8, -4.1)		14.4.2A
	LOCF	-16.8 (-28.0, -5.6)		-14.1 (-22.8, -5.4)		
LDL	MMRM		0.646		0.381	
	LOCF		0.738		0.464	
Males	MMRM	-2.9 (-15.4, 9.5)		-4.0 (-15.1, 7.0)		14.4.5A
	LOCF	-4.1 (-16.1, 7.8)		-3.1 (-13.6, 7.3)		
Females	MMRM	-17.7 (-32.8, -2.6)		-7.1 (-18.1, 3.8)		14.4.6A
	LOCF	-7.1 (-20.1, 5.8)		-8.5 (-18.6, 1.5)		

number in each subgroup at week 24 (% attrition from number randomized)[3]

	Method	**NS 2000/20**	**NS 1000/20**	**S20**
Males	MMRM	26 (18.8%)	37 (26.0%)	48 (5.9%)
	LOCF	32	50	51
Females	MMRM	14 (41.7%)	41 (29.3%)	42 (17.6%)
	LOCF	24	58	51

[1] Method: Both analyses use the mITT population without Study Site RU02. MMRM: Mixed model repeated measures with no imputation for missing values; separate analysis for males and females to get estimates and CI's. LOCF: Analysis of covariance with LOCF imputation as described for the efficacy analysis, with sex represented as a factor in the model.

[2] P-value of the interaction of gender in the comparison of NS dose to S dose (MMRM model was as described for

	NS 2000/20 vs. S20	NS 1000/20 vs. S20
the efficacy analysis, with the addition of Sex interaction term with visit date and study arm.		
[3]The number in each subgroup for the LOCF method is the number that was randomized in the mITT population without Study site RU02. The number in in each subgroup for the MMRM method is the number that remained at week 24. The percentage is the percentage of subjects who dropped out prior to week 24.		

TABLE 25 Results from the statistical analysis of non-HDL in Dose Group B

	Method[1]	NS 2000/40 vs. S80 Difference in means (95% CI)	NS 2000/40 vs. S80 NI criteria of 6.0% met?	NS 1000/40 vs. S80 Difference in means (95% CI)	NS 1000/40 vs. S80 NI criteria of 6.0% met?	Table Reference
Non-HDL	MMRM		p[2]=0.676		p=0.478	
	LOCF		p=0.631		p=0.930	
Males	MMRM	-1.5 (-9.6, 6.5)	No	-1.0 (-9.1, 7.2)	No	4.4.5A
	LOCF	-0.2 (-7.4, 7.0)	No	-0.3 (-7.6, 6.9)	No	
Females	MMRM	-1.4 (-10.7, 7.8)	No	-0.1 (-8.9, 8.8)	No	4.4.6A
	LOCF	-2.9 (-11.3, 5.5)	Yes	0.1 (-7.5, 7.8)	No	
LDL	MMRM		p=0.358		p=0.204	
	LOCF		p=0.257		p=0.896	
Males	MMRM	8.6 (-0.2, 17.5)	No	4.6 (-4.3, 13.5)	No	4.4.13A
	LOCF	9.3 (1.4, 17.2)	No	5.1 (-2.9, 13.1)	No	
Females	MMRM	4.6 (-5.5, 14.7)	No	5.3 (-4.4, 15.0)	No	4.4.14A
	LOCF	2.3 (-6.9, 11.4)	No	4.3 (-4.0, 12.7)	No	

Number in each subgroup at Week 24 (% attrition from number randomized) [3]

		NS 2000/40	NS 1000/40	S80
Males	MMRM	48 (18.6%)	46 (22.0%)	47 (20.3%)
	LOCF	59	59	59
Females	MMRM	32 (17.9%)	36 (30.8%)	43 (25.6%)
	LOCF	39	52	54

[1] Method: Both analyses use the mITT population without Study Site RU02. MMRM: Mixed model repeated measures with no imputation for missing values; separate analysis for males and females to get estimates and CI's. LOCF: Analysis of covariance with LOCF imputation as described for the efficacy analysis, with sex represented as a factor in the model.

[2] P-value of the interaction of gender in the comparison of NS dose to S dose (MMRM model was as described for the efficacy analysis, with the addition of Sex interaction term with visit date and study arm.

[3]The number in each subgroup for the LOCF method is the number that was randomized in the mITT population without Study site RU02. The number in in each subgroup for the MMRM method is the number that remained at week 24. The percentage is the percentage of subjects who dropped out prior to week 24.

4.2 Other Special/Subgroup Populations

No additional subgroups were evaluated.

5.2 Conclusions

The statistical test results of the SEACOAST study support the efficacy of Simcor (the niacin/simvastatin combinations) with respect to the primary efficacy endpoint, non-HDL. These results were consistent across several analysis methods and versions of the analysis database. The results of statistical tests do not support the efficacy with respect to the secondary lipid endpoint LDL, although the average LDL at week 24 was lower than baseline in the niacin-simvastatin combination arms. However, the efficacy with respect to other secondary lipid endpoints such as HDL and TG are supported from the statistical test results.

Low Dose Combination Product: In subjects receiving the 20 mg dose of simvastatin, adding 1000 mg of niacin produced an additional average lowering of non-HDL of 8.6% at week 24 as a percentage of baseline. Adding 2000 mg of niacin produced an additional average lowering of non-HDL of 14.5%. These changes were all statistically significant. The effect of adding niacin on LDL in subjects receiving the 20 mg dose of simvastatin was not statistically significant. However, subjects receiving the 20 mg dose of simvastatin combined with either dose of niacin had a greater average increase in HDL and a greater average decrease in TG than subjects receiving the 20 mg dose of simvastatin as monotherapy, and these differences were statistically significant.

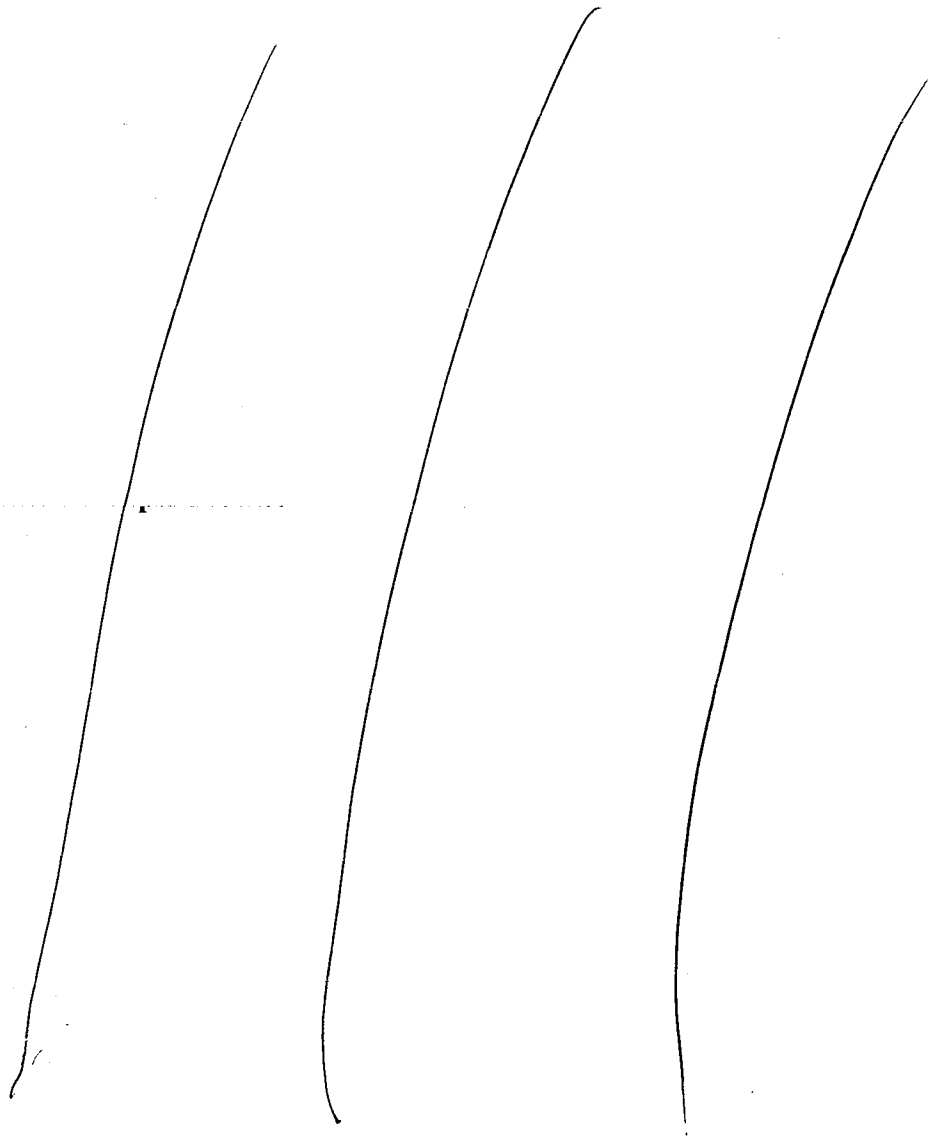
High Dose Combination Product: In subjects receiving the 40 mg dose of simvastatin combined with either 1000 mg or 2000 mg of niacin, the average change in non-HDL was non-inferior to the average change in non-HDL experienced by subjects receiving the 80 mg dose of simvastatin. The criterion for non-inferiority was not met for the LDL endpoint; in fact, subjects receiving the 40 mg dose of simvastatin and either dose of niacin appeared to have an LDL response that was inferior to that experienced by subjects receiving the 80 mg dose of simvastatin. However, subjects receiving the 40 mg dose of simvastatin and either dose of niacin had a greater average increase in HDL and a greater average decrease in TG than subjects receiving the 80 mg dose of simvastatin.

Gender Effect: Women receiving the 20 mg dose of simvastatin appeared to receive more benefit with the addition of niacin than men, on average, with respect to lowering non-HDL and LDL. This is similar to results from previous studies of niacin. However, the nominal p-values of gender by niacin interaction effects were not consistently less than 0.05, and the estimates were sensitive to the choice of imputation and analysis methods. In addition, the effect of gender was not as distinct for subjects taking niacin 1000 mg or 2000 mg combined with simvastatin 40 mg and compared to subjects taking simvastatin 80 mg.

Recommendations: This review (section 5.3) includes recommendations for the labeling text. There are no additional recommendations.

5.3 Recommendations for Labeling

The following are general recommendations for statistical aspects of the draft labeling text in the package insert.



1 Page(s) Withheld

1 Trade Secret / Confidential

_____ Draft Labeling

_____ Deliberative Process

Appendix A: Subjects who withdrew prior to completing the SEACOAST study

Group[1]	Arm	USubjID	Sex	Weeks on Drug (Database)[2]	Weeks on Drug (Listing 10.6.8)[3]	Reason for Discontinuing[4]	Type of AE from Listing 10.6.8	Flushing or related AE?
A	NS 1000/20	02401	M	2.3		WC		N
A	NS 2000/20	03701	F	3.6	1.9	AE	diabetes type 2	N
A	NS 2000/20	92059	F	3.6	4.3	Other	spontaneous abortion	N
A	NS 2000/20	90023	F	3.9	0.1	AE	headache	Y
A	NS 1000/20	00601	M	4.4	4.4	AE	flushing	Y
A	NS 1000/20	92057	M	4.6	4.1	AE	hyperglycemia	N
A	NS 2000/20	90015	F	4.6		WC		N
A	NS 2000/20	93125	F	5.1	5.3	AE	hypersensitivity NOS	Y
A	NS 1000/20	92005	F	5.3	4.3	AE	flushing	Y
A	NS 1000/20	93005	F	5.3		WC		N
A	NS 1000/20	90029	F	6.4		WC		N
A	NS 1000/20	92024	F	6.6	6.6	AE	flushing	Y
A	NS 1000/20	93081	F	6.6		WC		N
A	NS 1000/20	93035	F	7.9		WC		N
A	NS 1000/20	92010	M	8.0	1.1	AE	headache	Y
A	NS 1000/20	05721	F	8.9	9.0	AE	flushing	Y
A	NS 2000/20	92025	M	9.1		PV		N
A	NS 1000/20	90042	F	9.4	6.7	AE	headache	Y
A	NS 2000/20	00524	M	9.4	6.0	AE	flushing	Y
A	NS 1000/20	90028	M	10.1	10.1	AE	flushing	Y
A	NS 1000/20	90008	M	10.3		WC		N
A	NS 1000/20	03602	F	10.4	10.7	AE	fall	N
A	NS 1000/20	00220	M	11.3		PV		N
A	NS 2000/20	03601	F	12.1	11.9	AE	flushing	Y
A	NS 1000/20	93133	F	12.4		LFU		N
A	NS 2000/20	00221	M	13.0		PV		N
A	NS 2000/20	90009	F	13.7	12.4	AE	abdominal pain NOS	N
A	NS 1000/20	90003	M	15.4	15.1	AE	flushing	Y
A	NS 1000/20	90014	F	15.4		WC		N

Group	Arm	USubjID	Sex	Weeks on Drug (Database)	Weeks on Drug (Listing 10.6.8)	Reason for Discontinuing	Type of AE from Listing 10.6.8	Flushing or related AE?
A	NS 2000/20	92055	F	15.9	15.6	AE	flushing	Y
A	NS 2000/20	92007	M	16.1	12.9	AE	flushing	Y
A	NS 1000/20	92043	F	16.4		WC		N
A	NS 1000/20	93097	F	16.7	16.7	AE	allergic dermatitis	Y
A	NS 1000/20	00721	M	17.3		WC		N
A	NS 1000/20	02120	F	20.7		WC		N
A	NS 1000/20	92015	F	21.0	13.1	AE	flushing	Y
A	NS 2000/20	92012	F	27.9		PV		N
A	NS 1000/20	00201	M	.[5]		PV		N
A	NS 1000/20	04121	F	.		LFU		N
A	S20	93003	F	4.0		PV		N
A	S20	93123	F	5.1	2.1	AE	dyspepsia	N
A	S20	93122	F	5.3	1.9	AE	hypotension NOS	N
A	S20	04902	F	8.7		PV		N
A	S20	92032	F	11.6		WC		N
A	S20	06620	M	13.7		WC		N
A	S20	90019	F	18.3	13.0	AE	muscle pain	N
A	S20	04120	F	20.4	8.1	AE	constipation	N
A	S20	93031	M	25.3		WC		N
B	NS 1000/40	92511	F	2.6		AE		N
B	NS 1000/40	01456	M	3.9		PV		N
B	NS 1000/40	90551	M	3.9	1.1	AE	erectile dysfunction	N
B	NS 1000/40	90603	F	3.9		WC		N
B	NS 2000/40	02157	M	3.9	0.7	AE	flushing, itching	Y
B	NS 2000/40	05051	F	3.9		WC		N
B	NS 1000/40	02754	M	4.1		AE		N
B	NS 1000/40	04951	F	4.6	4.7	AE	rash	Y
B	NS 2000/40	01654	M	4.9	5.0	AE	shoulder pain	N
B	NS 1000/40	90608	F	5.6		WC		N

Group	Arm	USubjID	Sex	Weeks on Drug (Database)	Weeks on Drug (Listing 10.6.8)	Reason for Discontinuing	Type of AE from Listing 10.6.8	Flushing or related AE?
B	NS 2000/40	04057	M	6.0		WC		N
B	NS 1000/40	04651	F	6.7	6.0	AE	eczema	Y
B	NS 1000/40	04170	F	7.9	7.7	AE	urticaria	Y
B	NS 1000/40	06072	F	7.9		WC		N
B	NS 1000/40	02456	M	8.3		AE		N
B	NS 1000/40	03671	F	8.6	8.7	AE	flushing	Y
B	NS 1000/40	02652	F	8.9		Other		N
B	NS 2000/40	90544	M	10.1	8.6	AE	flushing	Y
B	NS 2000/40	06671	M	10.6	0.1	AE	flushing	Y
B	NS 1000/40	05974	M	11.1	10.1	AE	flushing	Y
B	NS 2000/40	02155	F	11.3	8.3	AE	abdominal pain	N
B	NS 1000/40	90556	M	11.6	9.1	AE	abdominal pain	N
B	NS 2000/40	90561	F	12.0	12.3	AE	flushing	Y
B	NS 2000/40	01454	M	12.1	8.3	AE	pruritis	Y
B	NS 1000/40	01752	F	13.0		AE		N
B	NS 2000/40	01955	F	13.1	8.6	AE	gastritis	N
B	NS 2000/40	01651	M	13.4	6.1	AE	allergic reaction	Y
B	NS 1000/40	02457	M	14.9		WC		N
B	NS 2000/40	00351	M	15.0		Other		N
B	NS 2000/40	04172	F	15.7	14.4	AE	diarrhea	N
B	NS 2000/40	01854	M	15.9	6.6	AE	itching	Y
B	NS 2000/40	04052	F	15.9		PV		N
B	NS 1000/40	90567	F	18.7		AE		N
B	NS 1000/40	90520	M	19.0	19.1	AE	cholecystitis	N
B	NS 2000/40	90594	M	19.7	18.7	AE	flushing	Y
B	NS 2000/40	00452	M	19.9		WC		N
B	NS 1000/40	02251	M	20.6	16.0	AE	allergic reaction	Y
B	NS 2000/40	02452	F	20.9	12.1	AE	hypothyroidism	N
B	NS 1000/40	01856	F	21.0	22.6	AE	small bowel obstruction	N

Group	Arm	USubjID	Sex	Weeks on Drug (Database)	Weeks on Drug (Listing 10.6.8)	Reason for Discontinuing	Type of AE from Listing 10.6.8	Flushing or related AE?
B	NS 1000/40	90564	M	22.0	18.6	WC	flushing	Y
B	S80	04552	M	3.0		Other		N
B	S80	90524	M	4.1	3.4	AE	flushing	Y
B	S80	90578	F	6.3		PV		N
B	S80	90546	F	6.9	7.0	AE	abdominal pain NOS	N
B	S80	02451	M	7.0	6.1	AE	rash	Y
B	S80	92501	F	7.0		WC		N
B	S80	90557	M	7.4		PV		N
B	S80	02758	F	7.9		Other		N
B	S80	02454	F	8.6	8.1	AE	elevated triglycerides	N
B	S80	02654	M	11.6		WC		N
B	S80	06071	M	11.6		WC		N
B	S80	05977	M	12.3		WC		N
B	S80	90528	F	16.4		WC		N
B	S80	90514	M	16.9	17.3	AE	esophagitis	N
B	S80	04554	M	17.6	17.7	AE	pain NOS	N
B	S80	01756	F	.		Other		N
B	S80	02570	F	.		Other		N

Notes:

[1] Subjects were in the mITT database, excluding Russian site RU02

[2] Number of weeks between last study drug taken and first study drug taken, calculated from the database ADSL.xtp

[3] Number of weeks on study drug, as reported by the applicant in data listing 10.6.8

[4] Reason for discontinuation: AE adverse events; WC withdrawal of consent; PV protocol violation; LFU lost to follow-up; Other

[5] If the number of weeks on study drug was missing, the value was imputed by the median value for the study arm (NS arms within groups were combined for calculating the median): S20: 9.4; NS 1000/20 and NS 2000/20: 11.6; S80: 7.9; NS 1000/40 and NS 2000/40: 11.2.

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