4. Subject had used an investigational study medication or participated in an investigational study within 30 days prior to the Screening Phase.
5. Subject had taken a study-prohibited medication (Section 5.4.7) within 2 weeks prior to the Screening Phase.
6. Subject had a history of any of the following assessed at the Screening Phase:
   - Active gallbladder disease within the preceding 12 months (cholecystectomy was allowed).
   - Chronic or acute pancreatitis within the preceding 6 months.
   - Liver disease (e.g., hepatitis B and/or C).
   - Persistent uncontrolled severe hypertension.
   - Bleeding diatheses.
   - Unstable angina, non-ST-segment elevation MI, or ST-segment elevation MI within the preceding 3 months.
   - Coronary artery bypass graft surgery within the preceding 6 months.
   - Angioplasty within the preceding 3 months.
   - Stroke or transient ischemic attack (TIA) within the preceding 3 months.
   - Deep vein thrombosis within the preceding 3 months.
   - Uncontrolled cardiac arrhythmias.
   - Acute or sub-acute peripheral artery disease occlusion.
   - Congestive heart failure (New York Heart Association [NYHA] class III or IV).
   - Unstable endocrine diseases.
   - Poorly-controlled type 1 or type 2 diabetes (glycosylated hemoglobin [HbA_{1c}] ≥ 9%).
   - Active cancer or a diagnosis of cancer within the last 5 years (excluding excised basal cell carcinoma).
   - Fibromyalgia, myopathy, rhabdomyolysis, unexplained muscle pain, and/or discontinuation of a statin medication due to myalgia.
7. Subject had any of the following abnormalities at any Screening or Qualification Visit:
   - Creatinine clearance <30 mL/min, as calculated by a central laboratory.
   - Creatine phosphokinase (CPK) elevation ≥ 3 x ULN.
   - HbA_{1c} ≥ 9%.
   - Active gout symptoms and/or uric acids level ≥ 1.3 x ULN.
   - Active peptic ulcer disease.
   - Active hepatitis, active liver disease.
   - Life expectancy <2 years.
8. At Screening, subject was receiving simvastatin >40 mg daily or equivalent (equivalent to >40 mg daily simvastatin defined as >80 mg daily atorvastatin, ≥ 20 mg daily rosuvastatin, and ≥ 10 mg/40 mg daily Vytorin).
9. Subject's LDL-C level was ≥ 250 mg/dL.

10. Subject's TG level was ≥ 500 mg/dL.
11. Subject demonstrated <75% adherence with simvastatin during the Run-in or Qualification Phases.

Prohibited Medications

Patients were not permitted to receive the following medications within 2 weeks of receiving any study medications or at any time during the course of the study:

- Amiodarone (Cordarone®).
- 3-isotretinoin (Accutane®).
- Cyclosporine (Sandimmune®, Neoral®).
- Danazol (Danocrine®).
- Nefazodone (Serzone®).
- Rifampin (Rifadin®).
- Oral erythromycin and/or any other oral macrolide antibiotic (e.g., clarithromycin [Biaxin®]).
- Telithromycin (Ketek®).
- Oral itraconazole (Sporanox®) and/or any other oral azole-type anti-fungal agent (e.g.,ketoconazole [Nizoral®], fluconazole [Diflucan®], and voriconazole [Vfend®]).
- Any preparation containing St. John's Wort (*Hypericum*).
- Any preparation containing *Ginkgo biloba*.
- Verapamil (Calan®, Verelan®, Isoptin®, Isoptin-SR®, Covera-HS®).
- Systemic androgens/anabolic steroids.
- Chronic (i.e., >2 weeks) systemic corticosteroids for life-threatening conditions.
- Human immunodeficiency virus (HIV) protease inhibitors (e.g., amprenavir [Agenerase®], indinavir [Crixivan®], saquinavir [Fortovase®, Invirase®], ritonavir [Norvir®], and nelfinavir [Viracept®]).

With Amendment 4, subjects taking the following lipid medications were not eligible for study participation:

- Atorvastatin ≥ 80 mg daily.
- Rosuvastatin ≥ 20 mg daily.
- Vytorin ≥ 10 mg/40 mg daily.

Lipid-modifying Medications

One day prior to receiving open-label simvastatin, subjects were required to discontinue the following lipid-modifying medications:

- Any HMG-CoA reductase inhibitor other than simvastatin provided by the Sponsor (e.g., atorvastatin [Lipitor®], fluvastatin [Lescol®], lovastatin [Mevacor®, Advicor®, Altoprev®], pravastatin [Pravachol®], and rosuvastatin [Crestor®]).

- Any fibric acid derivative (e.g., gemfibrozil [Lopid®], fenofibrate [TriCor®, Antara™], and clofibrate [Atromid-S®]).
- Any bile acid sequestrants (e.g., cholestyramine [Questran®, Questran Lite®], colestipol [Colestid®], and colesevelam [Welchol™]).
- Ezetimibe (Zetia®).
- Ezetimibe/simvastatin tablets (Vytorin™).
- Amlodipine/atorvastatin tablets (Caduet®).
- Any product (e.g., vitamin preparations) containing niacin or nicotinamide exceeding a 30-mg tablet daily dose.
- Cholestin (an over-the-counter product containing lovastatin, an active ingredient in Mevacor, or policosanol).

10.1.2.6 **Amendments**

The original protocol was finalized on 18 December 2003, and subsequently amended on 01 October 2004 (Amendment #1), 03 February 2005 (Amendment #2), 29 April 2005, (Amendment #3), and 03 October 2005 (Amendment #4). Major changes that affected the conduct of the study are summarized below:

AMENDMENT #1

- Added exclusion criteria limits for LDL-C >250 mg/dL.
- Revised lipid entry criteria to follow Therapeutic Options published in the NCEP Adult Treatment Panel III (ATP III) Report Update.
- Reduced diet compliance at Screening from 6 weeks to 4-6 weeks.
- Reduced simvastatin Run-in Phase from 6 weeks to 4 weeks. Qualification Phase provided additional time on simvastatin therapy to demonstrate lipid response.
- Extended study duration from 20 weeks to 24 weeks to meet drug exposure requirements.
- Latin American participation was added with an additional number of study sites to facilitate meeting the sample size requirements.

AMENDMENT #2

- Russian study participation was added.

AMENDMENT #3

- The primary efficacy endpoint was changed to non-HDL-C.
- Simvastatin 40-mg arm was removed from Dose Group A as no efficacy comparisons were to be made relative to this treatment group.
- Previously excluded treatment-naïve subjects with elevated non-HDL-C and LDL-C at goal were now eligible to skip the simvastatin 20 mg Run-in Phase and proceed directly to the Qualification Phase.
- Primary lipid criterion for enrollment in Dose Group B after qualification was changed from: elevated non-HDL-C and/or elevated LDL-C levels, to: elevated non-HDL-C levels with or without elevated LDL-C levels.
- Minimum Run-in Phase was changed from 4 weeks to 2 weeks while adding an

additional Qualification 4 visit to allow additional time to establish lipid stability, if needed.
- Sample size was increased from 525 to 640 subjects.

AMENDMENT #4
- Lipid entry criteria were changed to NCEP Treatment Goals. Both Treatment Goals and
- Options are within NCEP III Treatment Guidelines and consistent with standard medical practice.
- Upon completion of Dose Group B enrollment, subjects who were not treatment naive and had elevated LDL-C after completion of the simvastatin 20 mg Run-in Phase were to be discontinued, as the simvastatin 40 mg Run-in Phase was no longer available.
- Upon completion of Dose Group B enrollment, treatment-naïve subjects must have had screening LDL-C lipid levels within 40% of their target based on CHD risk factors (CHD/CHD risk equivalent ≥ 100 and ≤ 165, 2+ risk factors ≥ 130 and ≤ 215, 0-1 risk factors ≥ 160 and ≤ 250); upon completing a 20 mg simvastatin Run-in, these subjects were now eligible for Dose Group A randomization regardless of LDL-C levels, as long as their non-HDL-C levels remained elevated.
- Subjects receiving atorvastatin ≥ 80 mg, rosuvastatin ≥ 20 mg, and Vytorin ≥ 10/40 mg daily at study entry were to be excluded from study participation. For such subjects already randomized into the study, a basic lipid panel was to be collected between Weeks 18 and 20, and subjects were to be discontinued if the LDL-C value was elevated.

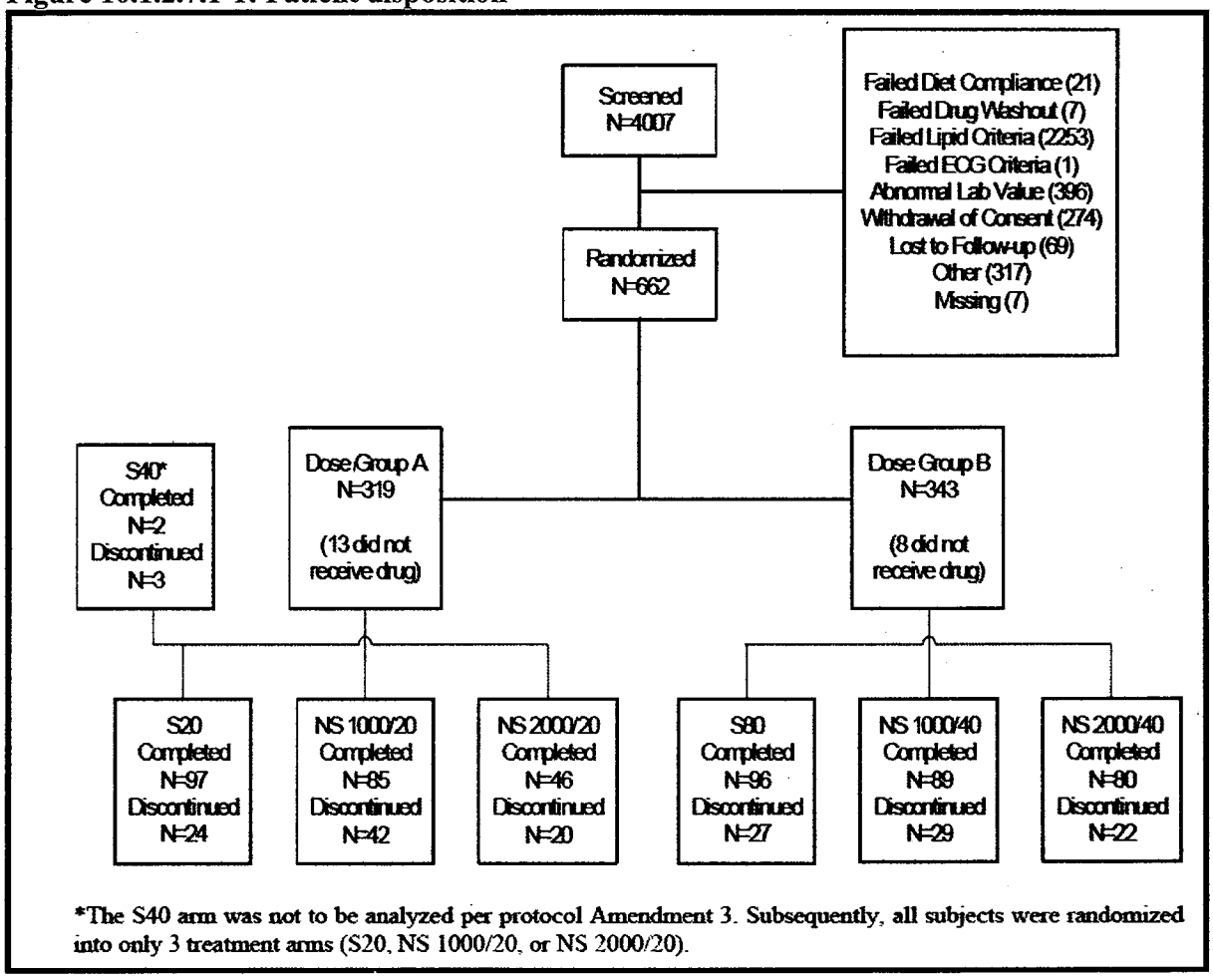
10.1.2.7 **Results**

10.1.2.7.1 Disposition

A total of 4007 patients were screened. Of these, 662 (16.5%) were randomized to study treatment. The most common reason for not being randomized was failure to meet lipid criteria. Of the 662 patients randomized, 641 patients received study medication. Of the 641 patients who received study medication, 167 (26%) withdrew from treatment over the 6 month study period. The most common reason for study discontinuation was AEs (%), primarily related to flushing episodes.

Five subjects were randomized to the S40 arm in Dose Group A (2 completed the study and 3 discontinued). Per Amendment #3, randomization into the S40 treatment arm was stopped and subsequent subjects were randomized into the 3 other treatment arms (S20, NS 1000/20, or NS 2000/20) per a new randomization schedule. The applicant did not analyze these five patients in the efficacy data; only the safety data included the patients in the discontinued S40 arm.

Figure 10.1.2.7.1-1: Patient disposition



The number of patients in each of the populations were as follows: 641 patients in the safety population, 588 patients in the m-ITT population (based on the exclusion of RU02 site) and 496 patients in the per protocol population. The table below is from the original NDA submission.

Table 10.1.2.7.1-2

Analysis Populations n (%)

Population	Number (%) of Subjects					
Dose Group A	**Total**	**S40**	**S20**	**NS 1000/20**	**NS 2000/20**	**NS Group A Overall**
Randomized	319	5	121	127	66	193
Safety[a]	306 (95.9)	5	114 (94.2)	123 (96.9)	64 (97.0)	187 (96.9)
m-ITT[b,c]	266 (83.4)	N/A	102 (84.3)	108 (85.0)	56 (84.8)	164 (85.0)
Per protocol[d]	226 (70.8)	N/A	94 (77.7)	86 (67.7)	46 (69.7)	132 (68.4)
Dose Group B	**Total**		**S80**	**NS 1000/40**	**NS 2000/40**	**NS Group B Overall**
Randomized	343		123	118	102	220
Safety[a]	335 (97.7)		119 (96.7)	116 (98.3)	100 (98.0)	216 (98.2)
m-ITT[b]	322 (93.9)		113 (91.9)	111 (94.1)	98 (96.1)	209 (95.0)
Per protocol[d]	270 (78.7)		96 (78.0)	91 (77.1)	83 (81.4)	174 (79.1)

[a] Subjects who had taken at least 1 dose of randomized study medication.

[b] Subjects in the 6 treatment arms with efficacy comparisons who had non-HDL-C data at baseline and at least 1 post-baseline visit.

[c] The m-ITT and per protocol populations are based on the dataset that excludes efficacy data for all 20 randomized subjects at Site RU02.

[d] Subjects in the m-ITT population who had no major protocol violation.

10.1.2.7.2 Demographics

Table 10.1.2.7.2-1: Demographics and baseline characteristics- Dose Group A

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)

BASELINE CHARACTERISTIC SUMMARY STATISTIC	S20 N=121	NS 1000/20 N=127	NS 2000/20 N=66	NS GROUP A OVERALL N=193
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)
≥2 risk factors	42 (34.7)	36 (28.3)	20 (30.3)	56 (29)
0-1 risk factors	9 (7.4)	17 (13.4)	10 (15.2)	27 (14)
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 10.1.2.7.2-2: Demographics and baseline characteristics- Dose Group B

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				
CHD and CHD risk equivalent	94 (76.4)	92 (78.0)	77 (75.5)	169 (76.8)
≥2 risk factors	27 (22)	23 (19.5)	22 (21.6)	45 (20.5)
0-1 risk factors	2 (1.6)	3 (2.5)	3 (2.9)	6 (2.7)

BASELINE CHARACTERISTIC SUMMARY STATISTIC	S80 N=123	NS 1000/40 N=118	NS 2000/40 N=102	NS GROUP B OVERALL N=220

BASELINE CHARACTERISTIC SUMMARY STATISTIC	S80 N=123	NS 1000/40 N=118	NS 2000/40 N=102	NS GROUP B OVERALL N=220
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)

10.1.2.7.3 Efficacy Findings

10.1.2.7.3.1 Primary Endpoint: Change from baseline in non-HDL at Week 24

Dose Group A (Simvastatin 20 mg vs. Simcor 1000/20 mg vs. Simcor 2000/20 mg) used a superiority approach to the statistical analysis. At week 24, non-HDL was reduced by -22.5% in the 2000/20 mg Simcor group as compared to -13.9% reduction in the 1000/20 mg group versus a -7.4% reduction in the simvastatin 20 mg group, $p<.05$.

Dose Group B (Simvastatin 80 mg, Simcor 1000/40 mg, Simcor 2000/40 mg) used a non-inferiority statistical approach. At week 24, non-HDL-C was reduced by -17.1% in the 2000/40 mg Simcor group; -11.3% in the Simcor 1000/40 mg group and -10.1% in the simvastatin 80 mg group. The Simcor 2000/40 and 1000/40 mg were non-inferior and at least as good as simvastatin 80 mg.

10.1.2.7.3.2 Secondary Endpoints: Change from baseline in other lipid parameters

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.

10.1.2.7.4 Safety Findings

10.1.2.7.4.1 Deaths
No deaths occurred during the study.

10.1.2.7.4.2 Other Serious Adverse Events
A brief summary of the narratives that were provided for the SAEs is shown in the table below:

Table 10.1.2.7.4-2: Patient narratives for SAEs

PATIENT ID# AND ARM	AGE	SEX	RELEVANT HISTORY	PREFERRED TERM	TREATMENT DAY	OUTCOME
Dose Group A						
92023 Simvastatin 20mg	59	Male	Hypercholesterolemia; Hypertension	Coronary artery atherosclerosis	25	Recovered
92040 Simvastatin 20 mg	67	Female	h/o previous CABG	Syncope/lipothymia	55	Recovered
93038 Simvastatin 20 mg	75	Female	Dyslipidemia, coronary heart disease, myocardial infarction, stable angina pectoris	Atrial fibrillation Coronary artery disease aggravated Myocardial infarction	104	Recovered
03603 Simvastatin 40 mg	74	Female	Hypertension, s/p CABG, CHF, diabetes, hyperlipidemia	Anemia NOS anaphylactic shock, Atrial fibrillation	144	D/C med Dropped out of study
03602 Simcor 1000/20 mg	72	Female	Dyslipidemia, hypertension, type 2 diabetes	Fall	75	D/C med Dropped out of study
93092 Simcor 1000/20 mg	48	Male	Dyslipidemia, hypertension	Transient Ischemic Attack	21	Recovered
92029 Simcor 2000/20 mg	68	Male	Dyslipidemia, hypertension,, type 2 diabetes	Cerebral ischaemia	110	Recovered
92059 Simcor 2000/20 mg	35	Female	Dyslipidemia,	Abortion spontaneous	30	Dropped from study due to pregnancy

Dose Group B						
02153 Simvastatin 80 mg	55	Male	Depression, L4/L5 bulging disc s/p microdiscectomy, h/o cyclobenzaprine use, cocaine and alcohol abuse	Depression Hallucination NOS Intervertebrial disc Herniation Tremors	22	Recovered
01053 Simvastatin 80 mg	57	Male		Cholecystitis NOS	182	Recovered
01856 Simcor 1000/40 mg	74	Female	Upper GI bleed, villous adenoma, h/o colonoscopy	Small intestinal obstruction NOS	158	Recovered and dropped out of study
90520 Simcor 1000/40 mg	57	Male	Type 2 Diabetes, dyslipidemia, myocardial infarction	Cholecystitis NOS Convulsions NOS Pyrexia Respiratory failure Sepsis NOS	134	Recovered and dropped out of study
90533 Simcor 1000/40 mg	40	Male	Dyslipidemia, type 2 diabetes, cigarette smoking	Ischemic optic neuritis	46	Recovered
90540 Simcor 1000/40 mg	53	Female	Type 2 diabetes, dyslipidemia, hypertension	Diabetic ulcer	126	Recovered
90564 Simcor 1000/40 mg	43	Male	Myocardial infarction, s/p CABG, hypertension, dyslipidemia	MI	165	Recovered and dropped out of study
04553 Simcor 2000/40 mg	69	Female	Hypertension, type 2 diabetes, coronary artery disease	Colitis ischaemic Coronary artery disease aggravated	45 164	Recovered
05772 Simcor 2000/40 mg	58	Male	Hypertension, dyslipidemia	Coronary artery disease NOS	33	Recovered

10.1.2.7.4.3 Dropouts and Other Significant Adverse Events

During the randomized treatment phase, 3 patients in Dose Group A and 3 patients in Dose Group B had a discontinuation due to a serious adverse event.

Table 10.1.2.6.4.3-1 presents a summary of serious adverse events leading to withdrawal.

Table 10.1.2.7.4.3-1: Serious adverse events leading to permanent treatment discontinuation

PATIENT ID# AND ARM	AGE	SEX	RELEVANT HISTORY	PREFERRED TERM	TREATMENT DAY	OUTCOME
Dose Group A						
03603	74	Female	Hypertension, s/p	Anemia NOS	144	Recovered

Simvastatin 40 mg			CABG, CHF, diabetes, hyperlipidemia	anaphylactic shock, Atrial fibrillation		Dropped out of study
03602 Simcor 1000/20 mg	72	Female	Dyslipidemia, hypertension, type 2 diabetes	Fall	75	Recovered Dropped out of study
92059 Simcor 2000/20 mg	35	Female	Dyslipidemia,	Abortion spontaneous	30	Dropped from study due to pregnancy
Dose Group B						
01856 Simcor 1000/40 mg	74	Female	Upper GI bleed, villous adenoma, h/o colonoscopy	Small intestinal obstruction	158	Recovered and dropped out of study
90520 Simcor 1000/40 mg	57	Male	Type 2 Diabetes, dyslipidemia, myocardial infarction	Cholecystitis NOS Convulsions NOS Pyrexia Respiratory failure Sepsis NOS	134	Recovered and dropped out of study
90564 Simcor 1000/40 mg	43	Male	Myocardial infarction, s/p CABG, hypertension, dyslipidemia	MI	165	Recovered and dropped out of study

10.1.2.7.4.4 Treatment Emergent Adverse Events Reported

The most common treatment-emergent AEs (greater than 2% of Simcor treated patients), summarized by SOC and preferred term are shown in Table 10.1.2.6.4.4-1 below

Table 10.1.2.7.4.4-1: Number and percent of treatment-emergent AE occurring in greater than 2% of safety population

SYSTEM ORGAN CLASS PREFERRED TERM	SIMVASTATIN OVERALL (N=238) N (%)	SIMCOR DOSE A OVERALL (N=187) N (%)	SIMCOR DOSE B OVERALL (N=216) N(%)	SIMCOR OVERALL (N=403) N(%)
Any AE	**126 (52.9)**	**102 (54.5)**	**138 (63.9)**	**240 (59.6)**
Infections and infestations	**38 (16)**	33 (17.6)	**30(13.9)**	**63 (15.6)**
Urinary tract infection	**5 (2.1)**	6 (3.2)	**5 (2.3)**	**11 (2.7)**
Nasopharyngitis	**4 (1.7)**	4 (2.1)	**5 (2.3)**	**9 (2.2)**
Influenza	**9 (3.8)**	7 (3.7)	**2 (0.9)**	**9(2.2)**
Gastrointestinal				

SYSTEM ORGAN CLASS PREFERRED TERM	SIMVASTATIN OVERALL (N=238) N (%)	SIMCOR DOSE A OVERALL (N=187) N (%)	SIMCOR DOSE B OVERALL (N=216) N(%)	SIMCOR OVERALL (N=403) N(%)
disorders	**49 (20.6)**	23 (12.3)	**39 (18.1)**	**62 (15.4)**
Nausea	**10 (4.2)**	6 (3.2)	**7 (3.2)**	**13 (3.2)**
Diarrhea NOS	**7 (2.9)**	3 (1.6)	**9 (4.2)**	**12 (3.0)**
Gastritis NOS	**5 (2.1)**	6 (3.2)	**4 (1.9)**	**10 (2.5)**
Musculoskeletal and connective tissue disorders	**23 (9.7)**	**18 (9.6)**	**37 (17.1)**	**55 (13.6)**
Back Pain	5 (2.1)	5 (2.7)	**8 (3.7)**	**13 (3.2)**
Arthalgia	6 (2.5)	2 (1.1)	**8 (3.7)**	**10 (2.5)**
Myalgia	4 (1.7)	2 (1.1)	**6 (2.8)**	**8 (2.0)**
Skin and subcutaneous tissue	**10 (4.2)**	**9 (4.8)**	**29 (13.4)**	**38 (9.4)**
Pruritus	**0**	2 (1.1)	**11 (5.1)**	**13 (3.2)**
Vascular disorders	**17 (7.1)**	**21 (11.2)**	**16 (7.4)**	**37 (9.2)**
Flushing	4 (1.7)	16 (8.6)	**11 (5.1)**	**27 (6.7)**
Hypertension NOS	6 (2.5)	5 (2.7)	**4 (1.9)**	**9 (2.2)**
Investigations	**20 (8.4)**	**15 (8.0)**	**22 (10.2)**	**37 (9.2)**
Nervous system disorder	**27 (11.3)**	**13 (7.0)**	**21 (9.7)**	**34 (8.4)**
Headache	11 (4.6)	9 (4.8)	**9 (4.2)**	**18 (4.5)**
Respiratory, thoracic and mediastinal disorders	**9 (3.8)**	**9 (4.8)**	**19 (8.8)**	**28 (6.9)**
General disorders and administrative site conditions	**12 (5.0)**	**7 (3.7)**	**20 (9.3)**	**27 (6.7)**
Metabolism and	**12 (5.0)**	**10 (5.3)**	**10 (4.6)**	**20 (5.0)**

SYSTEM ORGAN CLASS PREFERRED TERM	SIMVASTATIN OVERALL (N=238) N (%)	SIMCOR DOSE A OVERALL (N=187) N (%)	SIMCOR DOSE B OVERALL (N=216) N(%)	SIMCOR OVERALL (N=403) N(%)
nutrition disorders				
Cardiac disorders	**3 (1.3)**	**4 (2.1)**	**12 (5.6)**	**16 (4.0)**
Injury, poisoning and procedural complications	**5 (2.1)**	**3 (1.6)**	**10 (4.6)**	**13 (3.2)**
Renal and urinary disorders	**9 (3.8)**	**4 (2.1)**	**5 (2.3)**	**9 (2.2)**
Eye disorders	**4(1.7)**	**2 (1.1)**	**6 (2.8)**	**8 (2.0)**

10.1.2.7.4.5 Other significant adverse events

Other significant adverse events include hepatic, skeletal muscle, and renal events. Examination of AEs suggestive of liver disturbances, such as elevations in ALT and hepatic dysfunction revealed no clinically significant symptom complex. No muscle-related AEs associated with CK >10 x ULN occurred. No AEs suggestive of clinically significant renal dysfunction occurred.

10.1.2.7.4.6 Study schedule

Table 10.1.2.7.4.6-1: Study schedule

	Screen	Run-In	Qual 1	Qual 2	Qual 3 - 4[1]	Wk 0 Random	Wk 4	Wk 8	Wk 12	Wk 24 or Term
Clinical Laboratory Studies:										
Serum Basic Lipid Panel (TC, TG, LDL-C, HDL-C)[2]	✔		✔	✔	✔		✔	✔	✔	✔
Special Serum Lipid Panel (Apo A-I, Apo B, LpA-I, hs-CRP, etc.)[2]						✔			✔	✔
Serum Chemistry[2, 3, 4] (TSH/T4)[5]	✔			✔			✔	✔	✔	✔
Whole Blood Hematology[2]	✔			✔		✔	✔	✔	✔	✔
Plasma PT, PTT	✔			✔					✔	✔
Whole Blood HbA_{1c}[2]	✔			✔					✔	✔
Serum and Urine Pregnancy Test[6]	✔			✔						✔
Urinalysis[7]	✔						✔	✔	✔	✔
Reference Samples						✔	✔	✔	✔	✔

Medication:										
Dispense and Collect Zocor/Double-Blind Study Medication, as appropriate		✔	✔	✔	✔	✔	✔	✔	✔	✔
Study Medication Adherence Check			✔	✔	✔	✔	✔	✔	✔	✔
Concomitant Medication Query			✔	✔	✔	✔	✔	✔	✔	✔
Current Medication Query	✔									
Other Assessments:										
Dietary Instructions and Logs Dispensed and Collected	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Adverse Event Query		✔	✔	✔	✔	✔	✔	✔	✔	✔
Aspirin/Flushing Logs Dispensed						✔	✔	✔	✔	
Aspirin/Flushing Logs Collected/ Reviewed							✔	✔	✔	✔
ECG				✔						
Informed Consent/HIPAA (HIPAA for US patients only)	✔									
Medical History Intake/Update	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Randomization Number Assigned						✔				
Physical Examination			✔							✔
Schedule Next Visit	✔	✔	✔	✔	✔	✔	✔	✔	✔	
Screening Number Assigned	✔									
Social History	✔					✔			✔	✔
Vital signs, Weight, Height[8]	✔					✔	✔	✔	✔	✔

[1]Qualification 3 or 4 Visit only for those who do not satisfy lipid stability criteria at Qualification. [2]12-hour fast prior to blood sample draw. [3]Creatinine clearance will be calculated by the central laboratories at Screening. [4]At Qualification 2 Visit, only AST/ALT and CPK will be drawn. [5]Measure at Qualification Visit 2 only if patient takes thyroid replacement therapy. [6]Serum pregnancy test only at Screening Visit completed for all women < 60 years old; Qualification 2 Visit and Week 24 urine pregnancy tests are for women of childbearing potential. [7]Urine collected at Weeks 4, 8, 12, and 24 only if clinically indicated. [8]Height will be measured only at Screening.

10.1.3 Appendix B

Study 019-02-03-CR: OCEANS

An Open-Label Evaluation of the Safety and Efficacy of a Combination of Niacin ER and Simvastatin in Patients with Dyslipidemia

Study initiation date: June 10, 2004
Study completion date: June 14, 2006

10.1.3.1 Objectives

Primary:

- To evaluate the safety of two Simcor titration regimens in subjects with primary type II hyperlipidemia or mixed dyslipidemia.
- To compare the two Simcor titration regimens with respect to the incidence of flushing up to and including Week 52.

Secondary:

- To evaluate efficacy based on changes from baseline in lipid endpoints, high-sensitivity C-reactive protein (hs-CRP), and NCEP lipid target achievement.

10.1.3.2 Endpoints

Primary efficacy measures:

- Incidence and severity of adverse events, abnormal laboratory values and physical exams. Safety variables include routine chemistry and hematology parameters, urinalysis, vital signs, physical examinations, and adverse events (AEs)
- The number and percent of patients with flushing in the two Simcor titration regimens

Secondary efficacy measures:

- The primary lipid endpoint was based on changes from baseline in non- HDL-C and the secondary endpoints on changes from baseline in LDL-C, HDL-C, Total-C, TG, Total-C:HDL-C ratio, LDL-C:HDL-C ratio, lipoprotein a (Lp[a]), apolipoprotein B (Apo B), apolipoprotein A-I (Apo A-I), lipoprotein A-I (Lp A-I), and lipoprotein A-I:A-II (Lp A-I:A-II).
- The number and percent of patients reaching NCEP ATP III target goals.
- Changes from baseline to Week 52 in high sensitivity C-reactive protein

10.1.3.3 Statistical and Analytical Plans
Analysis population: The following analysis sets were defined and utilized in the analysis and presentation of the data:

- **Randomized population:** all patients who were randomized into the study
- **Safety population:** all patients who took at least one dose of randomized study medication
- **m-ITT population (modified intention-to-treat):** patients who contributed non-HDL-C data at baseline and at least one post-baseline visit
- **Long-term m-ITT**: patients who contributed non-HDL-C data at baseline and at least one post-baseline visit beyond Week 24.
- **On-treatment m-ITT**: patients who were on or within two days of discontinuing Simcor therapy
- **On treatment long-term**: patients who were on or within two days of discontinuing Simcor therapy

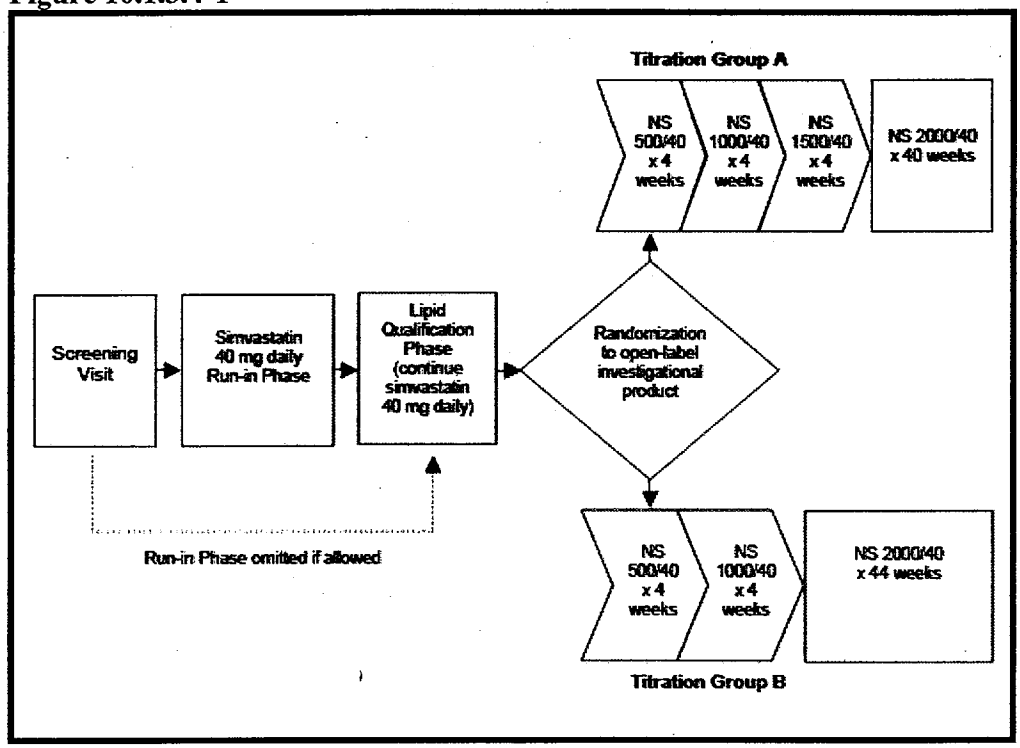
Table 10.1.3.3-1

Analysis Population (Randomized Subjects)			
	Titration Group A	**Titration Group B**	**Overall**
Randomized	262 (100)	258 (100)	520 (100)
Safety	257 (98.1)	252 (97.7)	509 (97.9)
m-ITT	251 (95.8)	245 (95.0)	496 (95.4)
Long-term m-ITT	136 (51.9)	145 (56.2)	281 (54.0)
On-Treatment m-ITT	232 (88.5)	231 (89.5)	463 (89.0)
On-Treatment long-term m-ITT	126 (48.1)	142 (55.0)	268 (51.5)

10.1.3.4 Study Design: This was a 52-week, open-label, multi-center, Phase III study 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 overall study design comprised of a 4 to 6 week Run-in Phase, a 1-2 week Lipid Qualification Phase, and up to a 52-week Treatment Phase. (Note: Protocol Amendment #4 shortened the treatment phase to 24 weeks once the number of patients exposed long-term was sufficient.) The figure below shows the overall study design.

Figure 10.1.3.4-1



During the screening visit, patients were identified for possible enrollment in the study if they met non-HDL-C inclusion criteria relative to their CHD risk status. (See table below) Patients who were treatment naïve were enrolled into the simvastatin Run-In Phase; those patients who had a prior history of taking simvastatin 40 mg were enrolled directly into the Lipid Qualification Phase.

Table 10.1.3.4-2

Non-HDL-C Study Eligibility Criteria

Risk Category [a]	non-HDL-C (mg/dL) level [b]	
	Non treatment-naive [c]	Treatment-naive
CHD or CHD risk equivalent	≥100 mg/dL	≥130 mg/dL
≥2 risk factors	≥130 mg/dL	≥160 mg/dL
0–1 risk factors	≥190 mg/dL	≥220 mg/dL

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

[b] Comparable LDL-C values are 30 mg/dL lower than non-HDL-C values.

[c] Original study design used entry criteria of ≥130, 160, and 190 mg/dL. With Protocol Amendment #2, the entry criteria were modified to be consistent with current standard medical practice (i.e., NCEP therapeutic options).

During the Run-in and Lipid Qualification Phases, patients received 40 mg of simvastatin. To continue on to randomization, patients must have demonstrated the following:

- Non-HDL-C stability: non-HDL-C values from two consecutive visits were within 15% of each other.
- Elevated non-HDL-C: average non-HDL-C value was elevated according to the non-HDL-C study entry criteria (Table 1).

Patients who met the criteria above were randomized to one of two titration regimens (Titration Group A or Titration Group B) for Simcor 2000/40 mg. Daily doses remained constant throughout the treatment phase once the maximum dosage was reached (Week 9 for Titration Group B and Week 13 for Titration Group A).

The dose-titration regimen for each titration group is outlined in Table 3. Patients were instructed to take the Simcor tablets by mouth once daily at bedtime with a low-fat snack. To help minimize flushing effects, patients were permitted to take aspirin, ibuprofen, or another non-steroidal anti-inflammatory drug (NSAID) approximately 30 minutes prior to Simcor.

Table 10.1.3.4-3

Dose-Titration Regimens Simcor Dose (mg niacin extended-release/mg simvastatin)				
Treatment	**Week 0-4**	**Week 5-8**	**Week 9-12**	**Week 13-52**
Titration Group A	500/40	1000/40	1500/40	2000/40
Titration Group B	500/40	1000/40	2000/40	2000/40

Randomization: The randomization scheme was a 1:1 distribution for the 2 titration groups with a block size of 4.

10.1.3.5 Inclusion and Exclusion Criteria

Inclusion Criteria:

1. Men and women 21 years of age or older.
2. Women were not to be pregnant or breastfeeding and not planning to become pregnant or to breast-feed during participation in this study. Women of childbearing potential must have committed to using oral contraception, intrauterine device (IUD), or a double-barrier method of contraception. Women using oral contraception must have done so for 3 months prior to the Run-in Phase, and continued to have done so for the duration of the study. To be considered not of childbearing potential, women must have been post-menopausal for at least 2 years or surgically sterile.
3. Subject was willing to participate for the duration of the study and agreed to and signed written ICFs and HIPAA forms.
4. Subject had primary type II hyperlipidemia (i.e., subject did not have hyperlipidemia caused by an uncontrolled, underlying disease state such as

hypothyroidism) or mixed dyslipidemia with non-HDL-C levels above target levels as specified in Table 1.

5. At Screening, the subject was described as ONE of the following **and** met the non-HDL-C screening eligibility criterion (Table 1):
   - The subject was not taking any lipid-modifying medication or had discontinued lipid modifying medication for ≥ 4 weeks prior to Screening (Treatment-naive); **or**
   - The subject was taking either simvastatin ≤ 40 mg/day or another lipid modifying medication for ≥ 4 weeks and was willing to discontinue such medication for the duration of the study (Non treatment-naive).
6. At least 4 weeks before the first dose of any study medication and for the duration of the study, subject was willing to withdraw from all study prohibited medications.
7. Subject was reasonably compliant with the NCEP TLC diet, as judged by study site personnel, for a minimum of 4 weeks prior to Qualification Visit 1, and was willing to comply for the duration of the study.
8. Subjects must have met ALL of the following laboratory criteria:
   - At Screening and/or Qualification:
     - TG levels <500 mg/dL.
     - - LDL-C <250 mg/dL.
     - - CPK <3 x upper limit of normal (ULN).
     - - Alanine aminotransferase (ALT) and AST <1.3 x ULN.
     - - Glycosylated hemoglobin (HbA_{1c}) <9%.
   - At Qualification:
     - Non-HDL-C Variability ≤ 15%. The non-HDL-C values of 2 consecutive blood samples drawn at Qualification Visit 1 and Qualification Visit 2 (and Qualification Visit 3, if necessary), taken 1 week apart, must have been within 15% of each other.
     - - Based on the average non-HDL-C values at Qualification Visits 1 and 2 (or Qualification Visits 2 and 3, if a third was required), non-HDL-C did not satisfy treatment goals.
9. Subjects demonstrated at least 75% adherence with simvastatin during the Run-in and/or Lipid Qualification Phases.

Exclusion Criteria

1. Subject had an allergy, hypersensitivity, or intolerance to niacin, statins, or their derivatives.
2. Subject consumed >2 alcoholic drinks per day (>14 alcoholic drinks per week) or had a history of substance abuse or dependency within 12 months prior to Screening.
3. Subject had untreated or unsuccessfully treated psychiatric disease.
4. Subject had used an investigational study medication or participated in an investigational study within 30 days prior to the Screening Phase.

5. Subject had taken a study-prohibited medication within 4 weeks prior to receiving the first dose of any study medication.
6. Subject had a history of any of the following:
   - Active gallbladder disease within the preceding 12 months (cholecystectomy was allowed).
   - Chronic pancreatitis or acute pancreatitis within the preceding 6 months.
   - Persistent uncontrolled severe hypertension.
   - Bleeding diatheses.
   - Unstable angina, non-ST-segment elevation myocardial infarction, or ST-segment elevation myocardial infarction within the preceding 3 months.
   - Coronary artery bypass graft surgery within the preceding 6 months.
   - Angioplasty within the preceding 3 months.
   - Stroke or transient ischemic attack within the preceding 3 months.
   - Deep vein thrombosis within the preceding 3 months.
   - Uncontrolled cardiac arrhythmias.
   - Acute or sub-acute peripheral artery disease occlusion.
   - Congestive heart failure (New York Heart Association class III or IV).
   - Unstable endocrine diseases.
   - Poorly controlled type 1 or type 2 diabetes ($HbA_{1c} \geq 9\%$).
   - Active cancer or a diagnosis of cancer within the last 5 years (excluding excised basal cell carcinoma).
   - Fibromyalgia, myopathy, rhabdomyolysis, unexplained muscle pain and/or discontinuation of a statin medication due to myalgia.
7. Subject had any of the following abnormalities at the Screening and/or any of the Qualification Visits:
   - An elevation of CPK $\geq$ 3 x ULN.
   - An elevation of AST or ALT $\geq$ 1.3 x ULN.
   - Creatinine clearance <30 mL/min, as calculated by central laboratory.
   - $HbA_{1c} \geq 9\%$.
   - Active gout symptoms and/or uric acid levels $\geq$ 1.3 x ULN.
   - Active peptic ulcer disease.
   - Active hepatitis, active liver disease (e.g., hepatitis B and/or C).
   - Life expectancy <2 years.
8. Subject had any health condition or laboratory abnormality that, in the opinion of the Principal Investigator, may have been adversely affected by the procedures or medications in this study.
9. At Screening, subject was receiving simvastatin >40 mg daily.
10. Subject's LDL-C level was $\geq$ 250 mg/dL.

10.1.3.6 Amendments and Post Hoc Changes

The original protocol, dated 18 December 2003, was amended on 19 January 2004 (Amendment #1), 23 November 2004 (Amendment #2), 14 July 2005, (Amendment #3), and 30 March 2006 (Amendment #4). Major changes that affected the conduct of the study are summarized below.

Amendment #1

No major changes

Amendment #2

- The sample size requirements were reduced from approximately 1,000 to 600 subjects.
- The treatment phase was extended from 48 weeks to 52 weeks to be consistent with international requirement.
- Lipid entry criteria and lipid goals were changed to reflect new treatment options published in the NCEP Report Update.
- The duration of the following assessments was changed from 6 weeks to 4 weeks: Run-in phase, washout phase for prohibited medications, the time for subjects to have been taking simvastatin 40 mg daily to qualify for exemption from the Run-in Phase, and the time subjects were NCEP TLC dietary compliant prior to entry into the study.
- An LDL-C level ≤ 250 mg/dL was added as an inclusion criterion.
- The analysis for the 2 titration groups was revised to be a descriptive comparison with respect to the cumulative incidence of flushing.
- For the efficacy analyses, the intention-to-treat (ITT) population was redefined as all subjects who had data for at least 1 post-baseline visit and had taken at least 1 dose of study medication.

Amendment #3

- The primary efficacy endpoint was changed from a co-primary efficacy endpoint of percent change from Baseline to Week 52 in LDL-C and non-HDL-C to a single primary efficacy endpoint of change from Baseline to Week 52 in non-HDL-C.
- The secondary efficacy endpoints were changed to percent change from Baseline to Week 52 in LDL-C, HDL-C, Total-C, TG, and Lp(a). All other efficacy endpoints were changed to percent changes from Baseline to each Visit at which the following were measured: LDL-C, non-HDL-C, Total-C, HDL-C, TG, Apo A-I, Apo B, Total-C:HDL-C ratio, LDL-C:HDL-C ratio, hs-CRP, Lp(a), Lp A-I, and Lp A-I:Lp A-II.
- The LDL-C escape criteria at Week 24 were changed from ≥ 70 mg/dL to ≥ 100 mg/dL for subjects with CHD or CHD risk equivalents and from ≥ 100 mg/dL to ≥ 130 mg/dL for subjects with ≥ 2 risk factors. Escape criteria for subjects with 0-1 risk factors remained ≥ 160 mg/dL.
- A study medication retitration schedule was added for subjects who interrupted dosing.

Amendment #4

- The duration of the study was reduced from 52 weeks to 24 weeks.

- Subjects who were receiving >24 weeks of treatment at that time were to be discontinued from the study.
- The study objective was clarified to reflect that OCEANS is a safety study. Efficacy evaluation was changed to a secondary objective.

Post Hoc Changes

The definition of HDL-C risk was changed from <30 mg/dL to 40mg/dL to reflect the updated NCEP targets. All efficacy assessments were performed on the on-treatment m-ITT and long-term m-ITT populations.

10.1.3.7 Results

10.1.3.7.1 Disposition

A total of 1,718 patients were screened. Of those, 520 patients were randomized to the study and 255 (49 %) of them discontinued the study. The table below shows the reasons for discontinuations in the randomized population.

After randomization, 57 (11.0%) patients were required to discontinue because they met Week 24 LDL-C escape criteria and 198 (38.1%) patients discontinued of their own volition. The proportion of subjects who discontinued was similar in both titration groups. The most common reason for discontinuation was an adverse event with 26.7% of patients in Titration Group A and 19.8% in Titration Group B. "Withdrawal of consent", "Lost to follow-up" and "Other" was also on the list for discontinuations.

Table 10.1.3.7-1

Table: Reasons for Discontinuation (Randomized Subjects)				
	Titration Group A		Titration Group B	
Reasons	**N=262 (%)**		**N=258 (%)**	
Total number of Discontinuations	137 (52.3)		118 (45.7)	
Adverse Event	70 (26.7)		51 (19.8)	
Withdrawal of Consent	22 (8.4)		23 (8.9)	
Lost to Follow-up	6 (2.3)		5 (1.9)	
Other	9 (3.4)		4 (1.6)	

10.1.3.7.2 Demographics

Table 10.1.3.7.2-1: Demographic and key baseline characteristics –randomized population

CHARACTERISTIC VARIABLE	TITRATION GROUP A (N=262)	TITRATION GROUP B (N=258)	OVERALL (N=520)
Age (years)			
Mean (SD)	59.1 (10.8)	60.0 (10.4)	59.6 (10.6)
Median	58.5	60.0	59.6
Range	24, 83	24, 85	24, 85
Age Category [n (%)]			
<65 years	173 (66)	170 (65.9)	343 (66)
>65 years	89 (34)	88 (34.1)	225 (43.3)
Sex [n (%)]			
Male	145 (55.3)	150 (58.1)	295 (56.7)
Female	117 (44.7)	108 (41.9)	225 (43.3)
BMI (kg/m^2)			
Mean (SD)	31.3 (6.9)	30.5 (6.0)	30.9 (6.5)
Median	29.8	29.5	29.6
Range	17.7, 67.2	18.2, 56.2	17.2, 67.2
Race [n (%)]			
Caucasian	225 (85.9)	204 (79.1)	429 (82.5)
Hispanic	17 (6.5)	21 (8.5)	38 (7.3)
Black	17 (6.5)	31 (12)	48 (9.2)
Asian	2 (0.8)	1 (0.4)	3 (0.6)
Other	1 (0.4)	1 (0.4)	2 (0.4)
CHD Risk Category [n (%)]			
CHD and CHD risk equivalent	180 (68.7)	162 (62.8)	342 (65.8)
≥2 risk factors	72 (27.5)	85 (32.9)	157 (30.2)
0-1 risk factor	10 (3.8)	11 (4.3)	21 (4.0)
Diabetes [n (%)]			
No	177 (67.6)	187 (72.5)	364 (70.0)
Yes	85 (32.4)	71 (27.5)	156 (30.0)
Lipid treatment at screening [n (%)]			
Naïve	84 (32.1)	87 (33.7)	171 (32.9)
Non-naive	178 (67.9)	171 (66.3)	349 (67.1)

10.1.3.7.3 Concomitant medications:

The majority (99%) of subjects used 1 or more concomitant medications during the study The most common concomitant medications were aspirin/NSAIDs, which were taken by over 50% of subjects overall. Other common (>10% of subjects overall) concomitant medications were multivitamin and mineral supplements (33.4%), metoprolol (19.4%), lisinopril (16.3%), atenolol (14.1%), metformin (13.9%), vitamin E (12.0%), hydrochlorothiazide (11.0%), and calcium (10.8%).

10.1.3.7.4 Efficacy Findings

Efficacy was assessed as a secondary objective in the OCEANS study. This reviewer will focus only on the following lipid variables: non-HDL-C, LDL-C, total-C, TG and HDL-C. Samples were collected on Weeks 4, 8, 12, 24, 32, 40 and 52. The results are as follows according to Table 10.1.3.7.4-1.

Table 10.1.3.7.4-1 Percent change from baseline on treatment m-ITT and long term m-ITT populations

Non-HDL-C (mg/dL)

m-ITT population	Baseline Value	Week 24 % change	Week 52 % change
n	**463**	**463**	**463**
Mean	147.2 (33.4)	−19.7 (23.8)	−16.3 (25.3)
Median	141.0	−22.2	−20.4
Q1, Q3	125.0, 163.5	−35.1, −7.8	−31.9, −4.3
Min, max	85.5, 302.0	−69.3, 106.3	−69.5, 117.0
Long-term m-ITT n	**268**	**268**	**268**
Mean	145.6 (33.0)	−26.2 (19.4)	−20.7 (23.4)
Median	139.3	−27.3	−24.2
Q1, Q3	124.3, 161.3	−37.1, −16.9	−34.3, −11.4
Min, max	87.0, 302.0	−69.3, 106.3	−69.5, 117.0

LDL-C (mg/dL)

m-ITT population	Baseline Value	Week 24 % change	Week 52 % change
n	**463**	**463**	**463**
Mean	114.6 (31.5)	−17.4 (25.7)	−12.5 (29.1)

Median	110.5	−21.0	−17.0
Q1, Q3	96.5, 126.5	−33.8, −4.6	−28.6, −1.3
Min, max	41.5, 261.5	−88.9, 94.7	−88.9, 216.7
Long-term m-ITT			
n	**268**	**268**	**268**
Mean	112.8 (29.7)	−23.7 (20.0)	−15.9 (28.1)
Median	108.8	−25.0	−19.3
Q1, Q3	96.5, 121.8	−35.7, −14.0	−30.7, −7.5
Min, max	42.5, 261.5	−71.2, 55.3	−71.7, 216.7

HDL-C (mg/dL)

m-ITT population	**Baseline Value**	**Week 24 % change**	**Week 52 % change**
n	463	463	463
Mean	47.0 (12.6)	22.3 (21.8)	23.9 (23.0)
Median	45.0	20.4	21.4
Q1, Q3	38.5, 53.5	6.9, 33.3	9.3, 35.0
Min, max	19.5, 120.5	−50.5, 149.3	−50.5, 152.1
Long-term m-ITT			
n	268	268	268
Mean	46.5 (11.7)	26.1 (22.3)	29.1 (23.7)
Median	44.5	23.9	26.5
Q1, Q3	38.5, 51.8	11.4, 36.1	13.5, 39.6
Min, max	19.5, 97.5	−22.9, 149.3	−24.2, 152.1

Total-C (mg/dL)

m-ITT population	**Baseline Value**	**Week 24 % change**	**Week 52 % change**

n	463	463	463
Mean	194.2 (36.4)	−9.3 (17.2)	−6.4 (18.2)
Median	188.5	−11.1	−7.7
Q1, Q3	171.0, 211.5	−20.5, −1.1	−17.6, 0.7
Min, max	126.5, 343.0	−53.7, 88.5	−55.4, 99.3
Long-term m-ITT			
n	268	268	268
Mean Median	192.1 (35.6) 186.3	−13.3 (14.6) −14.3	−8.5 (17.1) −10.2
Q1, Q3	168.0, 208.5	−22.3, −5.1	−18.9, −1.9
Min, max	126.5, 343.0	−50.3, 88.5	−55.4, 99.3

TG (mg/dL)

m-ITT population	Baseline Value	Week 24 % change	Week 52 % change
n	463	463	463
Mean	163.5 (74.7)	−24.7 (32.4)	−24.9 (32.3)
Median	149.5	−30.7	−31.1
Q1, Q3	109.5, 201.5	−47.7, −9.3	−48.1, −7.4
Min, max	40.0, 450.5	−77.0, 156.9	−83.9, 156.9
Long-term m-ITT			
n	268	268	268
Mean	163.9 (77.3)	−30.7 (30.0)	−31.3 (29.3)
Median	149.5	−35.9	−37.8
Q1, Q3	108.3, 199.0	−51.4, −13.5	−54.8, −11.8
Min, max	48.0, 450.5	−77.0, 146.6	−83.9, 66.0

After 24 weeks of study medication, 82% and 93% of subjects in the on-treatment m-ITT and on-treatment long-term m-ITT populations, respectively, had met their NCEP targets for non-HDL-C and/or LDL-C. This degree of control was maintained with long-term treatment over 52 weeks.

Table 10.1.3.7.4-2 Subjects Reaching NCEP Targets (m-ITT* and Long-term m-ITT*)

	Titration Group A (N=232)		Titration Group B (N=231)		Overall (N=463)	
m-ITT population	N	(%)	N	(%)	N	(%)
Baseline						
Non-HDL-C	105	(45.3)	104	(45.0)	209	(45.1)
LDL-C	106	(45.7)	111	(48.1)	217	(46.9)
Non-HDL-Ca and/or LDL-C	125	(53.9)	131	(56.7)	256	(55.3)
HDL-C risk (<40 mg/dL)	72	(31.0)	68	(29.4)	140	(30.2)
HDL-C negative risk (≥60 mg/dL)	25	(10.8)	32	(13.9)	57	(12.3)
Week 24						
Non-HDL-C	175	(75.4)	187	(81.0)	362	(78.2)
LDL-C	178	(76.7)	184	(79.7)	362	(78.2)
Non-HDL-Ca and/or LDL-C	186	(80.2)	193	(83.5)	379	(81.9)
HDL-C risk (<40 mg/dL)	31	(13.4)	31	(13.4)	62	(13.4)
HDL-C negative risk (≥60 mg/dL)	89	(38.4)	96	(41.6)	185	(40.0)
Final Visit						
Non-HDL-C	169	(72.8)	176	(76.2)	345	(74.5)
LDL-C	166	(71.6)	170	(73.6)	336	(72.6)
Non-HDL-Ca and/or LDL-C	178	(76.7)	185	(80.1)	363	(78.4)
HDL-C risk (<40 mg/dL)	27	(11.6)	27	(11.7)	54	(11.7)
HDL-C negative risk (≥60 mg/dL)	91	(39.2)	97	(42.0)	188	(40.6)

10.1.3.7.5 Safety Findings

10.1.3.7.5.1 Deaths

There was 1 death (Subject 03919) during the study. The patient was a 62-year-old man with a history of hyperlipidemia, hypertension, CAD, and angina. On randomization Day 68, the patient died at home in his sleep. The subject's death certificate documented the cause of death as atherosclerotic cardiovascular disease. At the time of death, the patient had completed approximately 1 week at a maximum dose of Simcor 2000/40. Total treatment duration on any dose of Simcor up to the time of death was approximately 10 weeks. Concomitant medications included: lisinopril 40 mg once daily, metoprolol 50 mg twice daily, aspirin 325 mg once daily, furosemide 40 mg once daily, nifedipine 60 mg once daily, sertraline 50 mg once daily, omeprazole 20 mg twice daily, and isosorbide dinitrate 20 mg 3 times daily as needed.

10.1.3.7.5.2 Other Serious Adverse Events

There were 40 out of 509 patients (7.9%) in the safety population who experienced 57 serious adverse events (SAEs). The table below lists all the serious adverse events.

Table 10.1.3.7.5.2.-1: Serious adverse events by Preferred Term

Preferred Term	Titration Group A N=257 (%)	Titration Group B N=252 (%)	Overall N=509 (%)
Total subjects with SAEs	**21 (8.2)**	**19 (7.5)**	**40 (7.9)**
Coronary artery disease aggravated	3 (1.2)	1 (0.4)	4 (0.8)
Myocardial infarction	1 (0.4)	3 (1.2)	4 (0.8)
Angina pectoris	2 (0.8)	1 (0.4)	3 (0.6)
Chest pain	1 (0.4)	2 (0.8)	3 (0.6)
Pneumonia NOS	1 (0.4)	1 (0.4)	2 (0.4)
Transient ischaemic attack	1 (0.4)	1 (0.4)	2 (0.4)
Acute coronary syndrome	0 (0)	1 (0.4)	1 (0.2)
Acute myocardial infarction	0 (0)	1 (0.4)	1 (0.2)
Atrial fibrillation	0 (0)	1 (0.4)	1 (0.2)
Cardio-respiratory arrest	1 (0.4)	0 (0)	1 (0.2)
Adrenal cyst	1 (0.4)	0 (0)	1 (0.2)
Blindness transient	0 (0)	1 (0.4)	1 (0.2)
Optic ischaemic neuropathy	1 (0.4)	0 (0)	1 (0.2)
Abdominal pain upper	1 (0.4)	0 (0)	1 (0.2)
Appendicitis perforated	0 (0)	1 (0.4)	1 (0.2)
Diverticulitis NOS	0 (0)	1 (0.4)	1 (0.2)
Gastric ulcer haemorrhage	1 (0.4)	0 (0)	1 (0.2)
Gastrointestinal ulcer haemorrahge	0 (0)	1 (0.4)	1 (0.2)
Cholecystitis NOS	1 (0.4)	0 (0)	1 (0.2)
Cellulitis	1 (0.4)	0 (0)	1 (0.2)
Haematoma infection	0 (0)	1 (0.4)	1 (0.2)
Drug toxicity NOS	0 (0)	1 (0.4)	1 (0.2)
Eye injury NOS	0 (0)	1 (0.4)	1 (0.2)
Incision site complication	1 (0.4)	0 (0)	1 (0.2)
Diabetic ketoacidosis	0 (0)	1 (0.4)	1 (0.2)
Bursitis	1 (0.4)	0 (0)	1 (0.2)
Localised osteoarthritis	1 (0.4)	0 (0)	1 (0.2)
Musculoskeletal chest pain	1 (0.4)	0 (0)	1 (0.2)
Rotator cuff syndrome	1 (0.4)	0 (0)	1 (0.2)
Breast cancer NOS	0 (0)	1 (0.4)	1 (0.2)

Preferred Term	Titration Group A N=257 (%)	Titration Group B N=252 (%)	Overall N=509 (%)
Lip and/or oral cavity cancer NOS	0 (0)	1 (0.4)	1 (0.2)
Carotid artery stenosis	0 (0)	1 (0.4)	1 (0.2)
Cerebellar infarction	1 (0.4)	0 (0)	1 (0.2)
Cerebrovascular disorder NOS	1 (0.4)	0 (0)	1 (0.2)
Convulsions NOS	1 (0.4)	0 (0)	1 (0.2)
Syncope vasovagal	1 (0.4)	0 (0)	1 (0.2)
Renal cyst NOS	1 (0.4)	0 (0)	1 (0.2)
Renal failure acute	1 (0.4)	0 (0)	1 (0.2)
Uterine prolapse	1 (0.4)	0 (0)	1 (0.2)
Arterial thrombosis limb	1 (0.4)	0 (0)	1 (0.2)
Arteriosclerosis	0 (0)	1 (0.4)	1 (0.2)
Deep vein thrombosis	0 (0)	1 (0.4)	1 (0.2)
Peripheral artery aneurysm	1 (0.4)	0 (0)	1 (0.2)

A brief summary of the narratives that were provided for the SAEs is shown in the table below:

Table 10.1.3.7.5.2-2: Patient narratives for SAEs

PATIENT ID#	AGE	SEX	RELEVANT HISTORY	PREFERRED TERM	TREATMENT DAY	OUTCOME
Titration Group A						
03902	80	Male	Hypertension, coronary artery bypass surgery X 2	Coronary artery disease aggravated Cholecystitis NOS	121 122	Recovered Recovered
03920	73	Male	Coronary artery disease, hypertension	Myocardial infarction	63	Recovered
00105	65	Male	Hypertension, diabetes mellitus, hyperlipidemia	Optic ischaemic neuropathy	46	Withdrew consent and discontinued study
06501	60	Female	Hypertension, coronary artery disease, peripheral vascular disease	Cerebrovascular disorder NOS	42	Discontinued study due to pruritus
07904	78	Female	Osteoarthritis, hypertension	Localised osteoarthritis	58	Recovered

09608	83	Female	Hypertension, varicosities in lower extremities	Cellulitis	139	Recovered
08411	71	Male	Adrenal cyst. Increased size of left kidney	Adrenal cyst	17	Withdrew consent and discontinued study
08424	83	Male	Coronary artery disease, myocardial infarction	Arterial thrombosis limb Peripheral artery aneurysm	51	Recovered Recovered
02502	46	Female		Abdominal pain upper		Recovered
04202	58	Female	Parkinson's disease, emphysema	Pneumonia NOS	36	Recovered
04901	43	Male	Myocardial infarction, coronary artery disease,	Angina pectoris Coronary artery disease Aggravated Incision site complication	71	Recovered
05404	59	Male	Coronary artery bypass graft,	Musculoskeletal chest pain	94	Discontinued study due to LDL not meeting treatment goals
05905	75	Male	Coronary artery disease, coronary artery bypass graft, type 2 diabetes mellitus	Cardiorespiratory arrest Cerebellar infarction Convulsions NOS	44 54 78	Discontinued study
03507	44	Male	Osteoarthritis, Baker's cyst, coronary artery bypass graft	Bursitis	247	Recovered
03511	68	Male	Coronary artery disease,	Angina pectoris Coronary artery disease aggravated	77	Recovered
08902	77	Female	Hypertension, transient ischemic attack	Rotator cuff syndrome Gastric ulcer	297 335	Unresolved

				haemorrhage		
03604	55	Male	Chronic renal insufficiency, congestive heart failure	Renal failure acute	328	Discontinued from study
07201	54	Female	Hypercholesterolemia, bilateral tubal ligation	Uterine prolapse	123	Discontinued from study due to not meeting lipid goals at Week 24
02801	66	Male	Coronary artery disease, myocardial infarction	Chest pain	3	Discontinued from study
08008	49	Male	Coronary artery disease, myocardial infarction,	Syncope vasovagal	173	Study medication titrated down to Simcor 1000/40
01301	65	Male	Hypertension, peripheral artery disease. cerebral infarcts	Transient ischemic attack	61	Recovered
Titration Group B						
03912	56	Male	Peptic ulcer disease, coronary artery disease	Gastrointestinal ulcer	26	Discontinued from study due to event
03919	62	Male		Arteriosclerosis		Died
04809	71	Female		Deep vein thrombosis		Recovered
04011	33	Female	Type 1 diabetes mellitus, transient ischemic attack	Diabetic ketoacidosis	105	Recovered
05601	76	Female	Coronary artery disease, hypertension,	Chest pain Myocardial infarction	16 28	Discontinued from study due to protocol violation
00901	57	Female	Hypercholesterolemia, transient ischemic attack,	Chest pain	27	Discontinued from study due to flushing
08410	60	Male	Coronary artery disease, myocardial infarction	Appendicitis perforated	86	Recovered
08422	68	Male	Atrial flutter, coronary artery disease, prior cardioversion	Atrial fibrillation	255	Discontinued from study due to LFT elevations

04303	57	Male	Hypertension, diabetes mellitus	Acute coronary syndrome	219	Discontinued from study due to protocol violation
05503	77	Female	Coronary artery disease, peripheral vascular disease	Drug toxicity NOS Diverticulitis NOS	82 51	Recovered
01806	74	Female	Hypertension, hyperlipidemia, diabetes mellitus	Transient ischemic attack	298	Recovered
01817	68	Male	Coronary bypass graft X6, chronic obstructive pulmonary disease	Myocardial infarction	66	Discontinued study due to event
03501	55	Female	Coronary artery disease, myocardial infarction, hypertension	Angina pectoris Coronary artery disease aggravated	217 345	Recovered
00302	69	Female	Hypercholesterolemia	Breast cancer NOS Haematoma infection	5	Discontinued from study
07203	79	Male	Hypercholesterolemia,	Myocardial infarction Pneumonia NOS	75 81	Recovered
07219	68	Male	Tobacco use, coronary artery disease	Lip and/or oral cavity cancer NOS	277	Recovered
05810	82	Female	Coronary artery bypass graft, hypertension	Carotid artery stenosis	49	Recovered
02917	57	Male	Hyperlipidemia	Acute myocardial infarction	76	Recovered
08705	66	Male	Coronary artery disease, chemical injury to eye	Blindness transient Eye injury NOS	58	Unresolved

10.1.3.7.5.3 Dropouts and Other Significant Adverse Events

During the randomized treatment phase, 118 patients discontinued due to an adverse event. The most common adverse event leading to a discontinuation was flushing, followed by pruritus, and nausea. Table 10.1.2.6.4.3-1 presents a summary of adverse events leading to discontinuation.

Table 10.1.3.7.5.3-1: Adverse events leading to permanent treatment discontinuation

PREFERRED TERM	TITRATION GROUP A N=257 N (%)	TITRATION GROUP B N=252 N (%)	OVERALL N-509 N (%)
Any AE	**70 (27.2)**	**48 (19.0)**	**118 (23.2)**
Flushing	19 (7.4)	17 (6.7)	36 (7.1)
Pruritus	7 (2.7)	3 (1.2)	10 (2.0)
Nausea	4 (1.6)	0	4 (0.8)
Blood glucose increased	0	3 (1.2)	3 (0.6)
Glycosylated haemoglobin increased	2 (0.8)	1 (0.4)	3 (0.6)
Pruritus generalized	1 (0.4)	2 (0.8)	3 (0.6)
Rash NOS	3 (1.2)	0	3 (0.6)
Vertigo	1 (0.4)	1 (0.4)	2 (0.4)
Dyspepsia	1 (0.4)	1 (0.4)	2 (0.4)
Chest pain	3 (1.2)	1 (0.4)	2 (0.4)
Hypersensitivity NOS	1 (0.4)	1 (0.4)	2 (0.4)
ALT increased	1 (0.4)	1 (0.4)	2 (0.4)
Blood CPK increased	1 (0.4)	1 (0.4)	2 (0.4)
Hyperglycaemia	2 (0.8)	0	2 (0.4)
Muscle cramp	2 (0.8)	0	2 (0.4)
Urticaria NOS	2 (0.8)	0	2 (0.4)
Diabetes mellitus non-insulin dependent	0	2 (0.8)	2 (0.4)

10.1.3.7.5.4 All Treatment Emergent Adverse Events Reported

417 (81.9%) patients had 1571 adverse events overall. The most common treatment-emergent AEs, summarized by SOC for both titration groups are shown in Table 10.1.2.6.4.4-1 below:

Table 10.1.3.7.5.4-1: Treatment-Emergent Adverse Events Occurring in ≥3 % of the overall population by System Organ Class

SYSTEM ORGAN CLASS PREFERRED TERM	TITRATION GROUP A (N=257) N (%)	TITRATION GROUP B (N=252) N (%)	OVERALL N=509 N (%)
Any AE	**216 (84.0)**	**201 (79.8)**	**417 (81.9)**
Gastointestinal disorders	**54 (21.0)**	**58 (23.0)**	**112 (22.0)**
Nausea	19 (7.4)	13 (5.2)	32 (6.3)
Diarrhoea NOS	13 (5.1)	11 (4.4)	24 (4.7)
Vomiting NOS	12 (4.7)	8 (3.2)	20 (3.9)
General disorders and	**42 (16.3)**	**25 (9.9)**	**67 (13.2)**

SYSTEM ORGAN CLASS PREFERRED TERM	TITRATION GROUP A (N=257) N (%)	TITRATION GROUP B (N=252) N (%)	OVERALL N=509 N (%)
administration site conditions			
Oedema peripheral	12 (4.7)	7 (2.8)	67 (13.2)
Infections and infestations	**69 (26.8)**	**87 (34.5)**	**156 (30.6)**
Upper respiratory tract	21 (8.2)	20 (7.9)	41 (8.1)
infection NOS	8 (3.1)	16 (6.3)	24 (4.7)
Nasopharyngitis	10 (3.9)	12 (4.8)	22 (4.3)
Influenza	4 (1.6)	12 (4.8)	16 (3.1)
Sinusitis NOS	7 (2.7)	9 (3.6)	16 (3.1)
Investigations	**52 (20.2)**	**58 (23.0)**	**110 (21.6)**
Glycosylated haemoglobin increased	9 (3.5)	19 (7.5)	28 (5.5)
Blood glucose increased	12 (4.7)	13 (5.2)	25 (4.9)
Blood CPK increased	11 (4.3)	11 (4.4)	22 (4.3)
Musculoskeletal and connective tissue disorders	**62 (24.1)**	**55 (21.8)**	**117 (23.0)**
Arthralgia	13 (5.1)	18 (7.1)	31 (6.1)
Back pain	8 (3.1)	12 (4.8)	20 (3.9)
Pain in extremity	7 (2.7)	10 (4.0)	17 (3.3)
Nervous system disorders	**38 (14.8)**	**27 (10.7)**	**65 (12.8)**
Headache	10 (3.9)	13 (5.2)	**23 (4.5)**
Skin and subcutaneous tissue disorders	**50 (19.5)**	**36 (14.3)**	**86 (16.9)**
Pruritus	18 (7.0)	12 (4.8)	30 (5.9)
Rash NOS	9 (3.5)	7 (2.8)	16 (3.1)
Vascular disorders	**33 (12.8)**	**31 (12.3)**	**64 (12.6)**
Flushing	19 (7.4)	18 (7.1)	37 (7.3)

The most frequently affected SOC was Infections and infestations (30.6%), followed by Musculoskeletal and connective tissue disorders (23.0%), Gastrointestinal disorders (22.0% of subjects), and Investigations (21.6%).

Table 10.1.3.7.5.4-2: Treatment-Emergent Adverse Events Occurring in ≥3 % of Patients by Descending Frequency of Preferred Term

PREFERRED TERM	TITRATION GROUP A N=257 N (%)	TITRATION GROUP B N=252 N (%)	OVERALL N-509 N (%)
Any AE	**216 (84.0)**	**201 (79.8)**	**417 (81.9)**
Upper respiratory tract infection NOS	21 (8.2)	20 (7.9)	41 (8.1)
Flushing	19 (7.4)	18 (7.1)	37 (7.3)
Nausea	19 (7.4)	13 (5.2)	32 (6.3)
Arthralgia	13 (5.1)	18 (7.1)	31 (6.1)
Pruritus	18 (7.0)	12 (4.8)	30 (5.9)
Glycosylated haemoglobin increased	9 (3.5)	19 (7.5)	28 (5.5)
Blood glucose increased	12 (4.7)	13 (5.2)	25 (4.9)
Diarrhoea NOS	13 (5.1)	11 (4.4)	24 (4.7)
Urinary tract infection NOS	8 (3.1)	16 (6.3)	24 (4.7)
Headache	10 (3.9)	13 (5.2)	23 (4.5)
Nasopharyngitis	10 (3.9)	12 (4.8)	22 (4.30
Blood CPK increased	11 (4.3)	11 (4.4)	22 (4.3)
Vomiting NOS	12 (4.7)	8 (3.2)	20 (3.9)
Back pain	8 (3.1)	12 (4.8)	20 (3.9)
Oedema peripheral	12 (4.7)	7 (2.8)	19 (3.7)
Pain in extremity	7 (2.7)	10 (4.0)	17 (3.3)
Influenza	4 (1.6)	12 (4.8)	16 (3.1)
Sinusitis	7 (2.7)	9 (3.6)	16 (3.1)
Rash NOS	9 (3.5)	7 (2.8)	16 (3.1)

10.1.3.7.5.5 Other significant adverse events

Of particular clinical interest are flushing events. In OCEANS, patients recorded flushing events in flushing logs. The table below shows the number of patients who recorded flushing events in the two different titration groups.

Table 10.1.3.7.5.5-1 Number (%) of Subjects who Flushed (Safety Population)

	Titration Group A (N=257)		Titration Group B (N=252)		Overall (N=509)	
	CL	n (%)	CL	n (%)	CL	n (%)
Overall	249	168 (67.5)	246	183 (74.4)	495	351 (70.9)
Weeks 1-4	244	86 (35.2)	241	113 (46.9)	485	199 (41.0)
Weeks 5-8	225	81 (36.0)	227	105 (46.3)	452	186 (41.2)
Weeks 9-12	203	79 (38.9)	210	91 (43.3)	413	170 (41.2)
Weeks 13-24	190	81 (42.6)	187	68 (36.4)	377	149 (39.5)
Weeks 25-32	130	31 (23.8)	153	42 (27.5)	283	73 (25.8)
Weeks 33-40	99	35 (35.4)	114	36 (31.6)	213	71 (33.3)
Weeks 41-52	90	32 (35.6)	97	24 (24.7)	187	56 (29.9)

CL=number of subjects who completed aspirin/flushing logs; n=number of subjects who flushed; %=n/CL × 100.

In Weeks 0-4 and 5-8 Groups A and B received the same dose of Simcor (500/40mg in Week 0-4 and 1000/40 mg in Week 5-8). Group A reported 35.2 % flushing vs. Group B at 46.9% in Week 0-4. Similar percentages were reported in both groups in Week 5-8. Although Titration Group B had a higher dose of Simcor than Group A in Week 9-12 (2000/40 mg vs. 1500/40 mg), the percentages of flushing were similar to the previous weeks in the two groups indicating no difference in rates of flushing based on the titration regimen.

At least 70% of patients reported at least one flushing event. According to the data in the submitted NDA, the median number of days per week on which a flushing episode occurred was <1 day/week and ranged from 0.35 to 0.74 days. The median number of days per week on which moderate or severe flushing episodes occurred ranged from 0.14 to 0.47 days. The median number of days per week on which severe flushing episodes occurred ranged from 0.10 to 0.33 days.

Other significant adverse events include hepatic, skeletal muscle, and renal events. Examination of AEs suggestive of liver disturbances, such as elevations in ALT and hepatic dysfunction revealed no clinically significant symptom complex. There was one patient with an AST elevation later diagnosed with Hepatitis C. (See section on lab values) No muscle-related AEs associated with CK >10 x ULN occurred. No AEs suggestive of clinically significant renal dysfunction occurred.

10.1.3.7.5.6 Laboratory values

Chemistry

There were changes in the mean HbA1C and in the mean glucose values over the course of the study. The mean glucose value at baseline was 106 mg/dL; the mean glucose value increased to a maximum of 119 mg/dL at Week 12. The mean HgA1C at baseline was 6.0% and at the end of the study the mean HbA1C was 6.6%.

Table 10.1.3.7.6-1 Fasting Glucose (MG/DL) in the Safety Population

Arm	Statistic	Baseline	Week 4	Week 8	Week 12	Week 24
A	n	241	237	208	206	176
	Mean (SD)	105.8(26.9)	112.1(33.8)	119.0(43.0)	121.1(43.5)	118.2(40.8)
	Median	99.0	102.0	103.0	106.5	105.5
	Min, Max	58.0,224.0	41.0,308.0	50.0,320.0	74.0,349.0	62.0,300.0
B	n	n 239	230	213	205	185
	Mean (SD)	106.5(31.0)	110.1(28.7)	114.6(34.4)	115.9(34.7)	115.3(42.5)
	Median	100.0	102.0	105.0	106.0	106.0
	Min, Max	64.0,383.0	48.0,309.0	52.0,335.0	72.0,294.0	62.0,331.0
Overall	n	480	467	421	411	361

	Mean (SD)	**106.2(29.0)**	111.1(31.4)	116.8(38.9)	**118.5(39.4)**	116.7(4
	Median	99.0	102.0	104.0	106.0	106.0
	Min, Max	58.0,383.0	41.0,309.0	50.0,335.0	72.0,349.0	62.0,331.0

Fasting Glucose (MG/DL) Safety Population continued

Arm	Statistic	Week 40	Week 52
A	n	99	85
	Mean (SD)	109.1 (33.0)	106.0 (35.7)
	Median	102.0	97.0
	Min, Max	54.0, 262.0	60.0, 340.0
B	n	114	95
	Mean (SD)	106.5 (22.3)	106.1 (23.7)
	Median	100.0	99.0
	Min, Max	68, 210.0	77.0, 235.0
Overall	n	213	180
	Mean (SD)	107.7	106.1 (29.9)
	Median	100.0	98.0
	Min, Max	54.0, 262	60.0, 340.0

Table 10.1.3.7.6-2 HbA1C (%) in the Safety Population

Arm	Statistic	Baseline	Week 4	Week 8	Week 12	Week 24
Titration A	n	235	17	13	170	166
	Mean (SD)	6.0(0.7)	6.0(0.7)	5.9(0.8)	6.4(1.1)	6.4(1.0)
	Median	5.9	5.9	5.7	6.0	6.1
	Min, Max	4.6,8.5	4.9,7.8	5.0,7.7	4.8,12.6	5.0,10.4
Titration B	n	235	19	13	156	172
	Mean (SD)	6.0(0.7)	6.2(0.8)	6.5(0.7)6	6.3(1.0)	6.4(1.0)
	Median	5.9	6.0	.4	6.1	6.1
	Min, Max	4.2,8.9	5.3,8.0	5.5,7.8	4.9,10.6	4.6,10.9
Overall	n	470	36	26	326	338
	Mean(SD)	**6.0(0.7)**	6.1(0.7)	6.2(0.8)	6.4(1.1)	6.4(1.0)

	Median	5.9	5.9	6.0	6.1	6.1
	Min, Max	4.6, 8.5	4.9,8.0	5.0,7.8	4.8,12.6	4.6,10.9

Table: HbA1C (%) in the Safety Population continued

Arm	Statistic	Week 40	Week 52
Titration A	n	21	87
	Mean (SD)	6.7 (1.3)	6.3 (0.8)
	Median	6.1	6.0
	Min, Max	5.3, 10.6	5.4, 9.9
Titration B	n	24	96
	Mean (SD)	6.5 (1.0)	6.2 (0.7)
	Median	6.4	6.1
	Min, Max	5.2, 9.2	4.8, 10.0
Overall	n	45	183
	Mean(SD)	**6.6 (1.1)**	6.2 (0.8)
	Median	6.3	6.1
	Min, Max	5.2, 10.6	4.8, 10.0

Clinically significant changes in values of ALT and AST over the course of the study are summarized below.

Table 10.1.3.7.6-3 ALT elevations

	Titration Group A	Titration Group B	Overall
Patients with baseline measurement, n	262	258	520
>3X ULN at any visit, n (%)	2 (.8)	2 (.8)	4 (.76)
>5X ULN at any visit, n (%)	0	0	0

Four patients had ALT elevations >3XULN, but no patient had ALT >5XULN at any visit. One patient (03602) had clinically important elevations in ALT (> 3XULN on 2 consecutive visits greater than 48 hours apart). The patient was later diagnosed with hepatitis C.

10.1.3.7.5.9 Study schedule

	Screen	Run-in	Qual 1[a]	Qual 2[b] (Qual 3)	Week 0 Randomization	Week 4	Week 8	Week 12	Weeks 16 to 18	Week 24	Week 32	Week 40	Weeks 44 to 46	Final Visit or ET
AE Query		✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Aspirin/Flushing Logs Dispensed					✔	✔	✔	✔		✔	✔	✔		
Aspirin/Flushing Logs Collected/ Reviewed						✔	✔	✔		✔	✔	✔		✔
Basic Lipid Panel[c]	✔		✔	✔		✔	✔	✔		✔	✔	✔		✔
Whole Blood HbA_{1c}	✔			✔				✔		✔				✔
Whole Blood Hematology	✔			✔		✔	✔	✔		✔	✔	✔		✔
Serum and Urine Pregnancy Test[d]	✔			✔						✔				✔
Plasma PT, PTT	✔			✔								✔		✔
Plasma and Serum Reference Samples[e]					✔	✔	✔	✔		✔	✔	✔		✔
Serum Chemistry, including TSH and Total T4 [c,e]	✔			✔[f]		✔	✔	✔		✔	✔	✔		✔
Special Lipid Panel[c] (Apo A-I, Apo B, Lp(a), Lp A-I, Lp A-I:A-II, hs-CRP)					✔			✔			✔			✔
Urinalysis	✔				✔	✔		✔		✔	✔	✔		✔
Collect simvastatin/NS Study Meds			✔		✔	✔	✔	✔		✔	✔	✔		✔
Concomitant Med Query			✔	✔	✔	✔	✔	✔		✔	✔	✔		✔
Current Medication Query	✔													
Dietary Instructions and Logs Dispensed	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔		
Dietary Logs Collected[g]		✔	✔	✔	✔	✔	✔	✔		✔	✔	✔		✔
simvastatin/NS Study Med Dispensed		✔	✔		✔	✔	✔	✔		✔	✔	✔		
ECG			✔											
ICF/HIPAA	✔													
Medical History and Update	✔	✔	✔	✔	✔	✔	✔	✔		✔	✔	✔		✔
NCEP TLC Diet Compliance	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Physical Examination			✔[h]											✔
Randomization Number Assigned					✔									
Schedule Next Visit	✔		✔	✔	✔	✔	✔	✔		✔	✔	✔		
Screening Number Assigned	✔													
Social History	✔				✔			✔			✔			✔
Study Medication Adherence Check			✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔	✔
Telephone Contact									✔				✔	
Vital signs, Height[i], Weight	✔				✔	✔	✔	✔		✔	✔	✔		✔
Week 24 LDL-C Goal Evaluation										✔				

[a]Qualification Visit 1 was completed at Screening if subject was taking simvastatin 40 mg daily AND was NCEP TLC diet compliant for the prior 4 weeks. [b]Qualification Visit 3 was completed only if subject did not satisfy lipid criteria at Qualification Visits 1 and 2. [c]Twelve-hour fast was required prior to blood sample draw. [d]Serum pregnancy test only at Screening Visit for all women <60 years old, unless 2 years postmenopausal or surgically sterile; urine pregnancy test completed at the site for all women of childbearing potential <60 years old. [e]Creatinine clearance was calculated by CLCS at Screening. [f]Evaluated TSH and total T4 at Qualification Visit 2 only for subjects taking thyroid replacement therapy. [g]24-hour recall obtained at Screening. [h]Was performed at the Qualification Visit 2 if the Screening/Qualification Visit 1 was combined. [i]Height was measured only at Screening.
ET=Early Termination Visit; Qual=Qualification Visit

10.1.4 Appendix C:

Ongoing Study M10-013 (SUPREME)- 4 month safety update

A 12-Week, Open-Label, Multicenter Study to Compare the Lipid Effects of Niacin ER and Simvastatin (NS) to Atorvastatin in Subjects with Hyperlipidemia or Mixed Dyslipidemia

Study initiation date:
Study database cutoff date: July 13, 2007

10.1.4.1 Objectives
Primary: The primary objective of the SUPREME study is to demonstrate that Simcor, when compared to atorvastatin (Lipitor®), has superior high-density lipoprotein cholesterol (HDL-C) elevating effects at Week 12 in subjects with type II hyperlipidemia or mixed dyslipidemia who are currently off lipid-modifying therapy.

Secondary:
1. The secondary objectives are to compare changes from baseline to Week 8 in HDL-C, and from baseline to Weeks 8 and 12 in

- non-HDL-C,
- low-density lipoprotein cholesterol (LDL-C),
- total cholesterol (Total-C),
- LDL-C:HDL-C ratio,
- Total-C:HDL-C ratio,
- triglycerides (TG), and
- lipoprotein (a) (Lp[a]) with Simcor treatment versus atorvastatin treatment

2. To compare the proportions of subjects with LDL-C < 100 mg/dL, LDL-C < 130 mg/dL, HDL-C < 40 mg/dL, HDL-C ≥ 60 mg/dL, and Total-C:HDL-C ratio < 4.5 mg/dL at Week 12 for Simcor and atorvastatin treatment.

3. Safety was assessed with routine chemistry and hematology parameter measurements, physical examinations, pregnancy tests, vital signs assessments, flushing information assessments, and adverse events (AEs) analyses.

10.1.4.2 Endpoints
Primary efficacy measures
The primary variable was

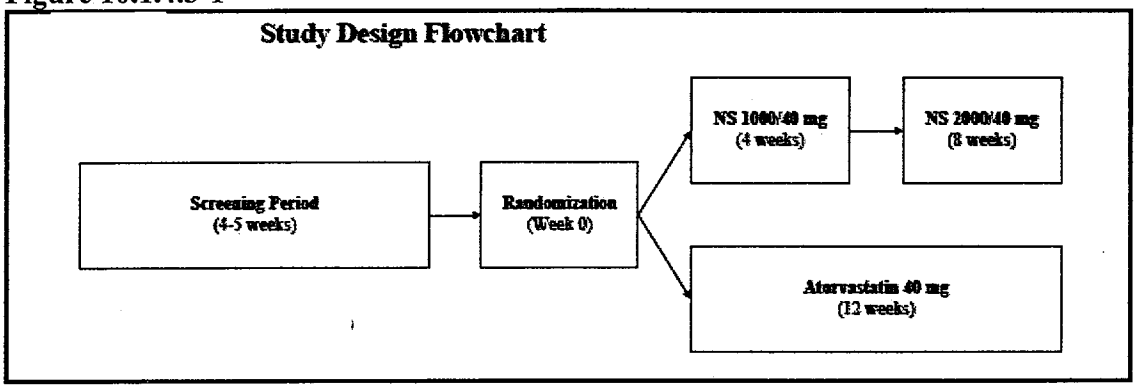
Safety variables include:

- Safety and tolerability, by evaluating the incidence and severity of AEs, abnormal laboratory values (hematology, clinical chemistry), vital signs, ECGs, and physical examinations

10.1.4.3 Study Design

This is an ongoing randomized, open-label, 12-week comparison of the lipid effects of Simcor 2000/40mg to atorvastatin 40mg in patients with hyperlipidemia or mixed dyslipidemia. Approximately 180 patients are planned to be enrolled in 25 sites. Patients meeting the eligibility criteria are randomized in a 3:2 ratio into one of two treatment arms, Simcor or atorvastatin. Patients in the Simcor treatment arm will be on Simcor 1000/40 for 4 weeks followed by Simcor 2000/40 for 8 weeks. The study design is as follows:

Figure 10.1.4.3-1



Eligible patients are enrolled into the Screening period for washout of their current lipid-modifying treatment and implementation of TLC diet. At the end of the Screening period, patients meeting the lipid criteria, diet criteria, and other requirements are randomized into the study. Patients receive the study medication per randomized treatment assignment for 12 weeks. Efficacy and safety assessments are conducted at protocol-specified time points.

The applicant submitted the following: subject disposition, demographic characteristics, and adverse events for Study M10-013. No efficacy data was included in the 4 month safety update. Furthermore, the safety data was not integrated into an ISS, as there was no ISS in the original NDA.

10.1.4.4 Results

10.1.4.4.1 *Disposition*

As of July 13, 2007, a total of 334 patients have been screened for enrollment into SUPREME. Of these subjects, 70 did not qualify for the study at initial screening, including 50 (15.0%) who did not meet the inclusion/exclusion criteria and 1 (0.3%) who failed screening due to an adverse event.

Two hundred sixty-four patients have entered into the screening washout period. Eighty-four patients (31.8%) did not meet the eligibility criteria for randomization, 5 patients (1.9%)

withdrew consent, 2 patients (0.8%) were lost to follow-up, and 116 patients (43.9%) remain active in the washout period.
Fifty-seven patients have been randomized to treatment groups: 33 to Simcor and 24 to atorvastatin.

10.1.4.4.2 *Demographics*

Table 10.1.4.4.2-1: Demographic and baseline characteristics – randomized patients

BASELINE CHARACTERISTIC SUMMARY STATISTIC	SIMCOR N=33	ATORVASTATIN N=24
Age		
Mean	54	51
Min, max	30, 89	31, 74
Sex		
Male [N (%)]	11 (33.3%)	11 (45.8%)
Female [N (%)]	22 (66.7%)	13 (54.2%)
Race		
Caucasian [N (%)]	28 (84.8%)	20 (83.3%)
Black [N (%)]	4 (12.1%)	1 (4.2%)
Asian [N (%)]	0	3 (12.5%)
American Indian [N (%)]	1(3.0%)	0

10.1.4.4.3 *All Treatment Emergent Adverse Events Reported*

Table 10.1.4.4.4.3-1: Number and percent of Simcor patients who had a treatment-emergent adverse event

SYSTEM ORGAN CLASS PREFERRED TERM	SIMCOR 2000/40MG, N=33 N (%)	ATORVASTATIN 40MG, N=24 N (%)
Any adverse event	**4 (12.1%)**	**0**
Gastrointestinal disorders	**1 (3%)**	**0**
Diarrhea	1 (3.0%)	
Infections and infestations	**1 (3.0%)**	**0**
Tooth infection	1 (3.0%)	
Injury, poisoning and procedural complications	**1 (3.0%)**	**0**
Clavicle fracture	1 (3.0%)	
Rib fracture	1 (3.0%)	
Vascular disorders	**1 (3.0%)**	**0**
Flushing	1 (3.0%)	

No treatment-emergent SAEs were reported for randomized subjects in either treatment

group. The safety information presented in this 4-month Safety Update, consisting of information from the open-label Simcor SUPREME study, is consistent with the safety findings previously reported in the original NDA 22-078. No new safety signals have been identified to date in this ongoing open-label study.

10.1.1 Appendix D

Drug Use Database Descriptions

Verispan, LLC: Vector One®: Total Patient Tracker (TPT)

Verispan's Total Patient Tracker is a national-level projected audit designed to estimate the total number of unique patients across all drugs and therapeutic classes in the retail outpatient setting.

TPT derives its data from the Vector One® database which integrates prescription activity from a variety of sources including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems. Vector One® receives over 2 billion prescription claims per year, which represents over 160 million patients tracked across time.

Verispan, LLC: Vector One®: Verispan Concurrency (VOCON)

Data used in VOCON is derived from Verispan's Vector One® database. The Vector One® database integrates prescription activity from a variety of sources, including national retail chains, mail order pharmacies, mass merchandisers, pharmacy benefits managers and their data systems, and provider groups. Vector One® receives over 2 billion prescription claims annually, representing over 160 million unique patients. Vector One® receives approximately half the of retail prescriptions dispensed nationwide. Verispan obtains all prescriptions from approximately one-third of the reporting stores and a significant sample of prescriptions from the remaining stores.

VOCON allows users to measure and evaluate concurrent drug therapy usage in unique patients during a selected time period using four scenarios. These scenarios are (in order of most to least restrictive): Same day fills, overlapping days supply, overlapping days supply with % grace period, fills during the same time period.

The VOCON module provides unprojected patients counts. Nationwide projections are not available.

Verispan, LLC: Physician Drug & Diagnosis Audit (PDDA)

Verispan's Physician Drug & Diagnosis Audit (PDDA) is a monthly survey designed to provide descriptive information on the patterns and treatment of diseases encountered in office-based physician practices in the U.S. The survey consists of data collected from approximately 3,100 office-based physicians representing 29 specialties across the United States that report on all patient activity during one typical workday per month. These data may include profiles and trends of diagnoses, patients, drug products mentioned during the office visit and treatment patterns. The data are then projected nationally by physician specialty and region to reflect national prescribing patterns.

Verispan uses the term "drug uses" to refer to mentions of a drug in association with a diagnosis during an office-based patient visit. This term may be duplicated by the number of diagnosis for which the drug is mentioned. It is important to note that a "drug use" does not necessarily result in prescription being generated. Rather, the term indicates that a given drug was mentioned during an office visit.

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/s/

Iffat N Chowdhury
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Eric Colman
2/15/2008 12:44:48 PM
MEDICAL OFFICER

6/27/07

MEMORANDUM

Filing Meeting: June 14, 2007
NDA 22-078 Original NDA
Simcor® (niacin extended-release and simvastatin)
500mg/20mg, 750mg/20mg, 1000mg/20mg
Abbott Laboratories
Iffat N. Chowdhury, MD

Letter date: April 17, 2007
Date received: April 17, 2007
PDUFA date: February 17, 2008

In NDA 22-078, the applicant has requested approval of Simcor® (niacin extended-release and simvastatin) 500mg/20mg, 750mg/20mg and 1000mg/20mg tablets for "use in patients with primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia." The applicant states that Simcor® is a fixed dose combination of drugs that are widely prescribed. 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. Simvastatin is a HMF-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 CV events.

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.

List of related INDs/NDAs:

IND/NDA #	**Drug**
IND 65,187	Simcor (niacin ER/simvastatin)
NDA 20-381 & IND 34,613	Niaspan (niacin ER)
NDA 21-248 & IND 56,027	Advicor® (niacin ER/lovastatin)
NDA 19-766	Zocor®
DMF [redacted]	Simvastatin

A **pre-IND 65,187 teleconference** was held on November 12, 2002 to discuss study designs and nonclinical, biopharm and CMC requirements. A Phase 1 study, CP-03-012004 has been conducted to evaluate to evaluate two different 20mg simvastatin — formulations on the same 500 mg niacin ER — used in Advicor. (Formulation NS-1 was chosen for future studies and no serious adverse events were associated with this trial). Two other Phase 1 studies are included in NDA22-078. Two Phase 3 clinical studies ("SEACOAST" and "OCEANS") began in 2004 and both were completed in 2006 and are the main studies comprising NDA 22-078. A **pre-NDA 22-078** meeting was held on September 26, 2006.

This Original NDA is an electronic submission containing 3 Phase 1 studies and 2 Phase 3 studies.

- **SEACOAST** was a Phase 3, double-blind, randomized, parallel-arm, active -controlled, 24-week treatment duration, multicenter clinical trial. The objectives of this study were to evaluate the efficacy and safety of NS (niaspan/simvastatin {Simcor}) by comparing 2 doses of NS (2000/20, 1000/20) relative to monotherapy with simvastatin 20 mg and 2 doses of NS (2000/40, 1000/40) relative to monotherapy with simvastatin 80 mg in subjects with primary type II hyperlipidemia or mixed dyslipidemia. The primary efficacy endpoint was the percentage change from baseline in non-HDL among treatment groups. The secondary endpoint was to compare the changes from baseline in LDL, HDL, TC, TG, Lp(a), Apo B, apolipoprotein A-1, and other parameters. SEACOAST was planned to be conducted in 477 subjects; however, the applicant enrolled 662 subjects at 129 sites in Russia, Argentina, Chile, Colombia and the United States.

- **OCEANS** was an open label, uncontrolled study in which subjects with primary type II dyslipidemia and mixed dyslipidemia were run-in on simvastatin 40 mg and then, if non-HDL remained elevated, were randomized to one of two titration regimens and maintained on NS therapy for up to 52 weeks. The titration schedule is displayed below.

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 primary objective of the study was to evaluate the long-term safety of NS 2000/40 mg in the population. The secondary objective was to study the incremental effect of chronic combination therapy with NS 2000/40 mg versus a simvastatin 40 mg treated baseline on lipid parameters. Phase 3, 52-week treatment duration, multicenter, open-label, randomized, parallel-group study. 509 subjects received the study medication at 71 sites in the United States.

Applicant requests included in NDA: three (3) years of marketing exclusivity

Labeling: The sponsor submitted both clean and annotated draft Package Insert and draft Patient Package Insert labeling for Simcor with clean Word and pdf versions.

Pediatric waiver: A request for a full waiver of pediatric studies (i.e. for all pediatric age groups) was submitted to IND 65,187 (letter date October 26, 2006). HFD-510 granted a full pediatric waiver in the regulatory letter dated December 7, 2006.

User Fee: The User Fee payment amount for NDA 22-078 is $896,200.00.

Efficacy Data:

SEACOAST: At week 24 in group A: Non-HDL was reduced by -22.5% in the 2000/20 NS group as compared to -13.9% reduction in the 1000/20 mg group versus a -7.4% reduction in the simvastatin 20 mg group. Thus, NS 2000/20 and 1000/20 demonstrated dose-related significant reductions in the primary endpoint that were greater than for simvastatin 20 mg.

At week 24, in group B: Non-HDL was reduced by -17.1% in 2000/40 mg NS group; -11.3% in the 1000/40 mg group; and -10.1% in the simvastatin 80 mg group. NS 2000/40 and 1000/40 were non-inferior and therefore, at least as good as simvastatin 80 mg.

Safety Data:

SEACOAST: There were no deaths. Overall 59.6% of subjects treated with NS and 53% of subjects treated with simvastatin experienced a total of 631 and 343 AEs, respectively. The most frequent AEs were flushing: NS: 6.7% and simvastatin 1.7%. Overall, 2.7% of NS patients and 2.5% of simvastatin patients reported serious AEs. A total of 13.6% NS-treated and 6.7% simvastatin treated subjects overall discontinued due to AEs. No subject had 2 or more consecutive AST or ALT values greater than 3 x ULN during the course of the study. No subject treated with NS had a CPK elevation >5 x or >10 x ULN; 1 subject treated with simvastatin 80 had a CPK elevation that was >10 x ULN.

Efficacy Data:

OCEANS: The interpretations of the results is limited by the open-label, uncontrolled nature of the OCEANS study. At week 52: Non-HDL was reduced by -24%; LDL was reduced by -19%; HDL was increased by -27%; TG was reduced by -38%.

Safety Data:

Oceans: Overall, 82% of subjects reported at least one AE. There were 23% of subjects who discontinued due to AEs. There was one death due to CV disease not considered related to treatment. One subject had persistent AST elevation >3X ULN; this subject was diagnosed with hepatitis C. There were no reports of myopathy. There were no subjects with CPK values >10x ULN. Overall, 71% of subjects experienced flushing in this study and most episodes (up to 86%) were mild in intensity. The percentage of subjects who discontinued the study due to flushing was 7% and not different between the titration groups.

Site Inspections:
A DSI consult was requested for site inspections for the controlled trial SEACOAST.

Financial Disclosures: Forms 3454 were submitted with the application.

Assessment:
Fileability: From a clinical standpoint, this NDA is fileable. (see Attachment 1)

Requests:
1) A request has been made to the applicant to submit data regarding the number of patients screened, enrolled and discontinued by site/investigator. This data will help determine the sites inspected.

2) Please clarify the location in the NDA or submit a rationale for assuming the applicability of foreign data in the submission to the U.S, population.

Attachment 1: NDA: 22-0778 Clinical Filing Meeting Checklist

45 Day Filing Meeting Checklist
CLINICAL

ITEM	YES	NO	COMMENT
1) On its face, is the clinical section of the NDA organized in a manner to allow substantive review to begin?	X		
2) Is the clinical section of the NDA adequately indexed and paginated in a manner to allow substantive review to begin?	X		
3) On its face, is the clinical section of the NDA legible so that substantive review can begin?	X		
4) If needed, has the sponsor made an appropriate attempt to determine the correct dosage and schedule for this product (i.e. appropriately designed dose-ranging studies)?	X		
5) On its face, do there appear to be the requisite number of adequate and well-controlled studies submitted in the application?	X		
6) Are the pivotal efficacy studies of appropriate design to meet basic requirements for approvability of this product based on proposed draft labeling?	X		
7) Are all data sets for pivotal efficacy studies complete for all indications requested?			
8) Do all pivotal efficacy studies appear to be adequate and well-controlled within current divisional policies (or to the extent agreed to previously with the applicant by the Division) for approvability of this product based on proposed draft labeling?	X		
9) Has the applicant submitted line listings in a format to allow reasonable review of patient data? Has the applicant submitted line listings in the format agreed to previously by the Division?	X		
10) Has the applicant submitted a rationale for assuming the applicability of foreign data in the submission to the U.S. population?		X	
11) Has the applicant submitted all additional required case report forms (beyond deaths and drop-outs) previously requested by the Division)?	X		

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/s/

Iffat N Chowdhury
6/27/2007 11:41:24 AM
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