CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER:

NDA 22-078

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

CLINICAL PHARMACOLOGY REVIEW

NDA	22-078
Submission Date(s)	April 17, 2007
Brand Name	Simcor®
Generic Name	niacin extended-release and simvastatin
Reviewer	Sang M. Chung, Ph.D.
Team Leader	Sally Choe, Ph.D.
OCP Division	Clinical Pharmacology 2
OND Division	Metabolism and Endocrinology Products
Sponsor	Abbott Laboratories
Submission Type	Standard
Formulation Strength(s)	500mg/20mg, 750mg/20mg, and 1000mg/20mg Tablets
Indication	Treatment of primary hypertriglyceridemia [redacted] mixed dyslipidemia, and hypertriglyceridemia
Dosage & Administration	SIMCOR should be taken as a single daily dose at bedtime, with a low fat snack. The dosage range is 500/20 mg/day through 2000/40 mg/day. The recommended initial doses are 500 [illegible] 20- [illegible] day. SIMCOR dose should be increased based upon desired lipid effects and the individual tolerability. Doses of SIMCOR greater than 2000/40 mg daily are not recommended. If SIMCOR therapy is discontinued for an extended period of time, re-titration as tolerated is recommended.

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1 Executive Summary

1.1 Recommendation

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed NDA 22-078 for Simcor® (niacin extended-release/simvastatin fixed dose combination). 1000/20mg and 500/20mg strength tablets are acceptable from clinical pharmacology perspectives provided that the Agency and the sponsor agree on the final labeling. However, acceptability of 750/20mg strength tablet is pending on the clinical evaluation.

1.2 Phase IV Commitments

None

1.3 Summary of Clinical Pharmacology and Biopharmaceutics Findings

The sponsor has submitted the NDA 22-078 for Simcor® (niacin extended release and simvastatin) as a 505(b)(2) application referencing NDA 20-381 (Niaspan® for niacin ER) and NDA 19-776 (Zocor® for simvastatin).

The Office of Clinical Pharmacology / Division of Clinical Pharmacology 2 (OCP/DCP-2) has reviewed the acceptability of three strengths of this fixed-dose combination product, 1000/20mg, 750/20mg, and 500/20mg.

1. 1000/20 mg Strength: This strength has been evaluated in a relative bioavailability (BA) study (019-03-04-CP) and in the pivotal Phase 3 studies (SEACOAST and OCEANS) for its efficacy and safety. The relative BA study was a single-dose, randomized, open-label, 4-way crossover study in healthy subjects. This study compared the pharmacokinetics of niacin, simvastatin and simvastatin acid after Simcor® (2x1000mg/20mg tablets; NS), Niaspan® (2x1000mg tablets; NSP), Zocor® (2x20mg tablets; ZOC), or co-administration (NSP+ZOC) of Niaspan® (2x1000mg) and Zocor® (2x20mg) with a snack at bedtime. While the niacin relative BA was comparable among different treatments, AUCs of simvastatin and simvastatin acid after Simcor® administration increased by 23% (90% CI of 112-134) and 41% (90% CI of 129-155), respectively, compared to those after Zocor® alone. The medical officer, Dr. Iffat Chowdhury concluded that the exposure increases of simvastatin and simvastatin acid after Simcor® administration compared to those of Zocor® were not clinically significant. Please see Dr. Chowdhury's review for more details.

2. 500/20mg Strength: This strength has been evaluated in a pilot comparative BA study (CP-03-012004) and in a Phase 3 study (SEACOAST) where its safety and efficacy have been evaluated.

3. 750/20mg Strength: This strength has not been formally evaluated in any clinical trials other than as part of a titration scheme in a Phase 3 study (OCEANS). The sponsor has justified 750/20mg strength for approval based on the followings (Appendix 5.1):

- This strength was used for 4 weeks in a Phase 3 study as a part of titration scheme.
- Dissolution study results were not indicative of *in vivo* study results for simvastatin. The lower dissolution rate of simvastatin resulted in higher simvastatin exposure from Simcor® compared to those of Zocor®.

In conclusion, based on the relative bioavailability studies and Phase 3 clinical trials, the 1000/20mg and 500/20mg tablet strengths of Simcor® are acceptable from the clinical pharmacology perspective. However, 750/20mg tablet strength neither has been utilized in any clinical pharmacology studies nor qualifies for a biowaiver because formulation proportionality among three strengths has not been established and the in vitro dissolution profiles for simvastatin have not been proved to be indicative of in vivo exposure profiles. Therefore, acceptability of 750/20mg strength will be justified by the clinical evaluation.

2 Background

The sponsor conducted five clinical trials including three Phase 1 studies and two Phase 3 studies for the Simcor® development. The studies are briefly summarized in Table 1. The Study 019-03-04-CP was considered as the pivotal clinical pharmacology study because both formulation and drug interactions were evaluated in the study using the highest to-be-marketed (TBM) formulation. The TBM tablets were reformulated with butylated hydroxyl anisole (BHA) [redacted] in the [redacted] from the Phase 3 formulation. The sponsor conducted a bioequivalence (BE) study (019-04-05-CP) for comparability between the TBM formulation and the Phase 3 formulation but did not complete the bioequivalence assessment because the Agency and the sponsor agreed that the BHA addition was qualified as a biowaiver before the submission of NDA (correspondence dated June 1, 2006; Please see IND review in the Appendix 5.2). The Study CP-03-012004 was a pilot BA study to evaluate the comparability between an exploratory formulation and the Phase 3 formulation using 500/20mg strength.

Table 1 Summary of clinical trials

Study	No. of subjects	Study Design	Treatment Regimen
Phase I			
019-03-04-CP	44	single-dose, randomized, open-label, 4-way crossover study in healthy subjects	Treatment NS: two 1000/20 tablets Treatment NSP: two niacin ER 1000 mg tablets Treatment ZOC: two simvastatin 20 mg tablets Treatment NSP+ZOC: two niacin ER 1000 mg tablets + two simvastatin tablets
019-04-05-CP	44	single-dose, randomized, open-label, replicate (ABAB or BABA) 4-way, 2-treatment, crossover study in healthy subjects	Treatment A: two 1000/20 tablets (TBM) Treatment B: two 1000/20 tablets (Phase 3 formulation)
CP-03-012004	42	Single-dose, randomized, open-label, 3-way crossover	Treatment NS1: two 500/20 tablets (Phase 3 formulation)

		study in healthy subjects	Treatment NS2: two 500/20 tablets (exploratory formulation) Treatment NSP+ZOC: two niacin 500 mg tablets + two simvastatin 20 mg tablets
Phase 3			
SEACOAST (controlled study)	662	24-week, multinational, multicenter, randomized, double-blind, parallel-arm, active controlled study	Group A: daily doses of NS 1000/20, NS 2000/20, or 20 mg simvastatin Group B: daily doses of NS 1000/40, NS 2000/40, or 80 mg simvastatin
OCEANS (supportive study)	520	52-week, multicenter, randomized, open-label, parallel-group, uncontrolled study	Treatment for up to 52 weeks with NS daily, in 2 different titration regimens, to a maximum dose of 2000/40

3 Question Based Review

3.1 General Clinical Pharmacology

3.1.1 *What are the highlights of the properties of the drug or the formulation as they relate to clinical pharmacology review?*

- Niacin pharmacokinetic parameters

Niacin pharmacokinetics was estimated by plasma nicotine uric acid (NUA, a metabolite of niacin) Cmax and urinary excretion of metabolites and niacin. The study condition and primary niacin pharmacokinetic parameters for relative BA study were comparable to information abstracted from the original Niaspan® NDA as follows:

  - The parent compound, niacin, could only be measured sporadically primarily due to extensive first-pass metabolism after oral dosing.
  - After a series of meetings, it was decided that NUA in plasma would be used as a measure of rate of niacin absorption and the amount of niacin and metabolites (NUA, N-methylnicotinamide (MNA), and N-methyl-2-pyridone-5-carboxamide (2PY)) excreted in the urine as an estimate of the extent of absorption.
  - Food increases BA by 30% but there was no difference on BA between high fat meals and low fat snacks.
  - No formal BE studies were conducted but the comparative BA studies with different strengths were conducted under fed conditions with light snacks.
  - Current approved labeling states that "Niaspan® should be taken at bedtime after a low-fat snack".

- Simvastatin formulation

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

- Simcor® formulation

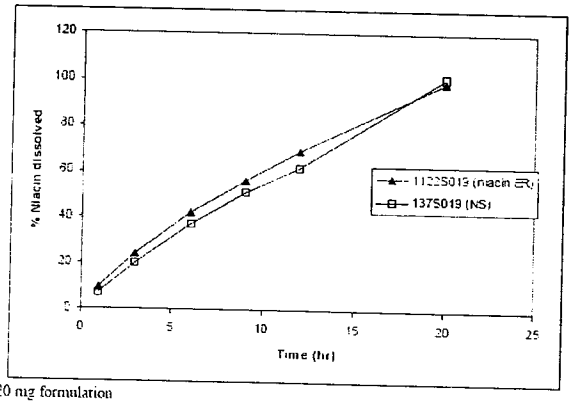
Simcor® is composed of niacin ER [redacted] simvastatin [redacted] The formulation proportionality among three strengths has not been established. Niacin ER consists of about 89% (w/w) of total tablet weight and the detailed components are in Table 2.

Table 2 Summary of Simcor® Components

Component	500 mg/20 mg	750 mg/20 mg	1000 mg/20 mg
Niacin	500	750	1000
[redacted]			
Povidone [redacted]			
Stearic Acid			
Simvastatin			
Butylated hydroxyanisole (BHA)			
[redacted]			
PEG			
Blue Opadry II 32K-10858			
Opadry [redacted] Clear			
Total Tablet Weight	**799.1**	**1086.6**	**1349.6**

- *In vitro* release characteristics of Simcor®

Niacin dissolution profiles were similar between Niaspan® and Simcor® (Figure 1), and similarity test of dissolution profiles met the sameness criteria for the Simcor® lower strengths (i.e., 500/20mg and 750/20mg) referencing 1000/20mg (Table 3).



NS: 1000 20 mg formulation

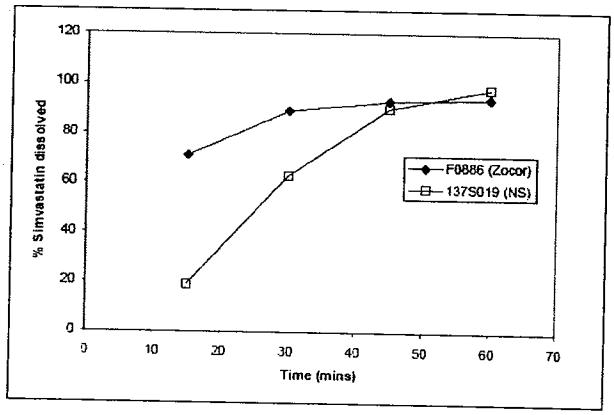
Figure 1 **Dissolution profiles of niacin from Niaspan® (niacin ER) and Simcor® (NS)**

Table 3 **Dissolution Profile Comparison based on Similarity (f_2) Factors (Lower Niacin ER/Simvastatin Containing BHA Tablet Strengths (500/20 and 750/20) versus the Highest Strength 1000/20) (Data Source: Report PESR060046-HR)**

Reference		Test		f_2
strength	Lot No.	Strength	Lot No.	
1000/20mg	137S019*	500/20mg	9F03/09*	62.26
			144S019	62.60
		750/20mg	147S019	57.56
	141S019	500/20mg	9F03/09*	61.30
			144S019	63.07
		750/20mg	147S019	56.01

*: Phase 3 formulations. Otherwise, TBM formulations.

Simvastatin dissolution profiles were not similar between Simcor® and Zocor® (Figure 2) and the similarity test of dissolution profiles did not meet the sameness criteria for the Simcor lower strengths referencing 1000/20mg (Figure 3 and Table 4).



NS: 1000/20 mg formulation

Figure 2 **Dissolution profiles of simvastatin from Zocor® and Simcor® (NS)**

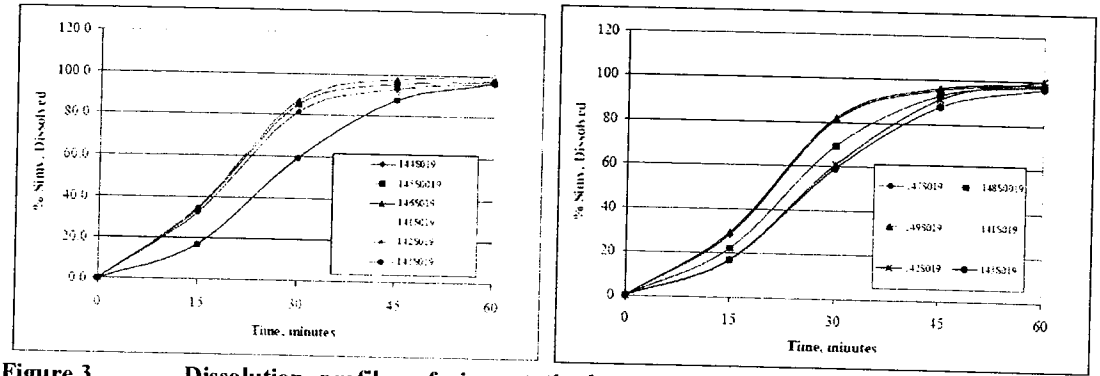


Figure 3 **Dissolution profiles of simvastatin between 500/20mg (Lots: 144S019, 145S019, 146S019)vs. 1000/20mg (Lots: 141S019, 142S019 and 143S019) (left panel) and 750/20mg (Lots: 147S019, 148S019 and 149S019) vs. 1000/20mg (Lots: 141S019, 142S019 and 143S019) (right panel)**

Table 4 **Dissolution Profile Comparison based on Similarity (f_2) Factors (Lower Niacin ER/Simvastatin Containing BHA Tablet Strengths (500/20 and 750/20) versus the Highest Strength 1000/20) (Data Source: Table 24, Section 3.2.P.2.2)**

N/S Tablet Strength	N/S Tablet Lot Number (n=12 for each lot)	Reference: 1000/20 N/S Tablet Lot Numbers (n=12 for each lot)	Similarity (f_1) and difference (f_2) factors calculation using the 1000/20 N/S Tablet with — BHA as the reference			
			f_1	Pass/Fail (NMT —)	f_2	Pass/Fail (NLT —)
500/20	144S019, 145S019, 146S019	141S019, 142S019, 143S019	25.0	Failed	36.7	Failed
750/20	147S019, 148S019, 149S019	141S019, 142S019, 143S019	16.5	Failed	46.1	Failed

NMT: Not More Than NLT: Not Less Than

3.1.2 *What is the relative bioavailability of niacin, simvastatin and simvastatin acid after Simcor® administration compared to those after Niaspan®, Zocor® or Niaspan®+Zocor® administration?*

A: 100/20mg Relative Bioavailability Study (019-03-034-CP)

The relative bioavailability was evaluated using a single dose, randomized, 4-way crossover study in 44 healthy volunteers with age between 40 and 70 (Study Protocol 019-03-04-CP). Washout period was at least 10 days. Treatments were administered with 240 ml water after a snack at bedtime (22:00) as follows:

- **NS (Treatment A):** 2000/40mg niacin ER/simvastatin (two tablets of 1000/20mg TBM formulation), Lot number 137S019
- **NSP (Treatment B):** 2000mg niacin ER (two tablets of 1000mg Niaspan®) Lot number 122S019
- **ZOC (Treatment C):** 40 mg simvastatin (two tables of 20mg Zocor®) Lot number F0886
- **NSP+ZOC (Treatment D):** 2000mg niacin ER (two tablets of 1000mg Niaspan®) and 40mg simvastatin (two tables of 20mg Zocor®) Lot numbers were 122S019 and F0886 for NSP and ZOC, respectively

Blood samples were collected within 30 min prior to dosing and 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 6, 8, 10, 14, 16 and 24 hours after dosing. Urine was collected in intervals of -24 to -18 to -12, -12 to -6, -6 to 0 hrs (i.e., prior to dosing) and 0 to 6, 6 to 12, 12 to 18, 18 to 24, 24 to 48, 48 to 72 and 72 to 96 hrs after dosing. Primary pharmacokinetic parameters estimation and the analysis of variance (ANOVA) were conducted using SAS®.

Forty-four subjects (21 males and 23 female) were enrolled in the study and the following data sets were excluded in the comparative BA assessment:

- Three subjects (Subject 0004, 0039, and 0040) did not finish the study and pharmacokinetic parameters were not included from the incomplete treatment(s),
- Two treatments were excluded for niacin and simvastatin due to emesis within 24 hours or within two times the median Tmax (Subject 0010 for Period 2, Treatment NSP+ZOC and Subject 0023 for Period 1, Treatment NS),
- Subject 0018 was excluded for niacin due to emesis at Period 2, Treatment NSP, and for simvastatin due to pre-dose concentration at Period 1, Treatment NS.

- Results of niacin relative bioavailability assessment

Mean NUA plasma concentration-time profiles by treatments were shown in Figure 4. Niacin pharmacokinetic parameters (plasma NUA Cmax and total urinary excretion) and relative BA were summarized in Table 5 and 6. Niacin exposure after Simcor® administration was BE to that after Niaspan® or co-administration of Niaspan® and Zocor® (Table 6).

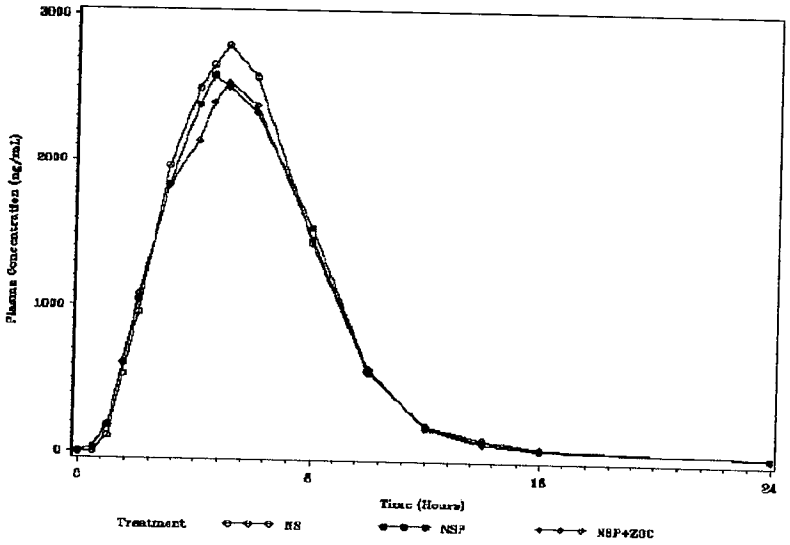


Figure 4 **Mean NUA plasma concentration-time profiles by treatment**

Table 5 **Mean (%CV) NUA pharmacokinetic parameters and urinary excretion of metabolites and niacin**

Pharmacokinetic Parameter	N	NS (A)	N	NSP (B)	N	NSP+ZOC (D)
Cmax (ng/mL)	42	3493.81(52.37%)	41	3500.98(44.16%)	41	3254.05(56.14%)
AUClast (ng.hr/mL)	42	16998.61(66.62%)	41	16512.41(56.03%)	41	16142.42(69.73%)
Tmax (hr)	42	4.88(27.78%)	41	5.12(34.43%)	41	5.23(29.85%)
Xu(-24-0h) (mg)	42	0.0019(648.1%)	40	0.0065(632.5%)	41	0.0000(.%)
Xu(0-96h) (mg)	41	299.91(51.56%)	40	279.58(55.14%)	41	271.23(61.01%)
% Fe(0-96h)Corr	41	10.24(51.56%)	40	9.55(55.14%)	41	9.26(61.01%)

NS: 2x1000/20 mg niacin ER/simvastatin.
NSP: 2 x 1000 mg niacin ER tablets.
ZOC: 2 x 20 mg simvastatin tablets.

Pharmacokinetic Parameter	N	NS (A)	N	NSP (B)	N	NSP+ZOC (D)
% Fe(0-96h)Total	41	54.07(22.11%)	40	54.50(19.08%)	41	53.63(22.93%)

NS: 2x1000/20 mg niacin ER/simvastatin.
NSP: 2 x 1000 mg niacin ER tablets.
ZOC: 2 x 20 mg simvastatin tablets.

Table 6 **Summary of statistical analysis for the niacin comparative BA**

Pharmacokinetic Parameter	Comparison	N	LS Mean (test)	N	LS Mean (ref)	LSM Ratio (90% Confidence Interval in %)
Cmax (ng/mL)	NS/NSP	42	3075.72	41	3208.74	0.9585 (88.16, 104.22)
	NS/NSP+ZOC	42	3075.72	41	2835.22	1.0848 (99.84, 117.88)
	NSP+ZOC/NSP	41	2835.22	41	3208.74	0.8836 (81.26, 96.08)
AUClast (ng.hr/mL)	NS/NSP	42	14269.82	41	14680.15	0.9720 (88.89, 106.30)
	NS/NSP+ZOC	42	14269.82	41	13469.21	1.0594 (96.95, 115.77)
	NSP+ZOC/NSP	41	13469.21	41	14680.15	0.9175 (83.90, 100.33)
% Fe(0-96h)Total	NS/NSP	41	54.39	40	54.81	0.9923 (93.37, 105.09)
	NS/NSP+ZOC	41	54.39	41	53.92	1.0087 (94.99, 106.75)
	NSP+ZOC/NSP	41	53.92	40	54.81	0.9838 (92.53, 104.23)

NS: 2x1000/20 mg niacin ER/simvastatin.
NSP: 2 x 1000 mg niacin ER tablets.
ZOC: 2 x 20 mg simvastatin tablets.

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Niacin plasma pharmacokinetic parameters were summarized in Table 7 and variability (%CV) was high.

Table 7 **Mean (%CV) niacin pharmacokinetic parameters**

Pharmacokinetic Parameter	N	NS (A)	N	NSP (B)	N	NSP+ZOC (D)
Cmax (ng/mL)	42	10917.02(96.44%)	41	11816.10(89.98%)	41	10174.39(91.03%)
AUClast (ng.hr/mL)	42	33361.59(123.0%)	41	35257.66(111.9%)	41	29978.88(122.3%)
Tmax (hr)	42	4.90(36.81%)	41	4.77(39.17%)	41	4.72(36.16%)
Xu(-24-0h) (mg)	42	0.0042(247.8%)	41	0.0099(389.3%)	41	0.0039(265.8%)
Xu(0-96h) (mg)	41	72.65(99.43%)	41	72.47(101.0%)	41	63.07(87.02%)
% Fe(0-96h)Corr	41	3.63(99.43%)	41	3.62(101.0%)	41	3.15(87.02%)

NS: 2x1000/20 mg niacin ER/simvastatin.
NSP: 2 x 1000 mg niacin ER tablets.
ZOC: 2 x 20 mg simvastatin tablets.

- Results of simvastatin relative bioavailability assessment

Mean simvastatin plasma concentration-time profiles by treatments were shown in Figure 5. Simvastatin pharmacokinetic parameters and relative BA were summarized in Table 8 and 9. Simvastatin Cmax and AUC after Simcor® were 17% and 23% higher than those after Zocor® alone. The higher simvastatin AUC (23%) after Simcor® seems to be from the formulation interaction (NS vs. NSP+ZOR; 12% increase) and the drug interaction (NSP+ZOC vs. ZOC; 9.5% increase).

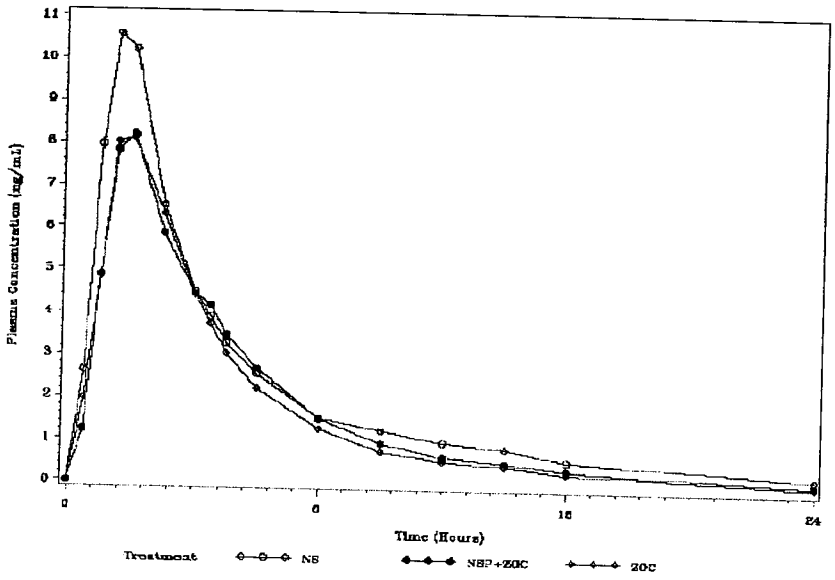

Figure 5 **Mean plasma concentration-time profiles of simvastatin by treatments**

Table 8 **Mean (%CV) simvastatin pharmacokinetic parameters**

Pharmacokinetic Parameter	N	NS (A)	N	ZOC (C)	N	NSP+ZOC (D)
Cmax (ng/mL)	42	13.28(61.07%)	42	10.94(59.15%)	42	11.05(54.70%)
AUClast (ng.hr/mL)	42	49.02(69.02%)	42	37.70(57.50%)	42	40.10(44.18%)
Tmax (hr)	42	1.99(92.36%)	42	2.13(46.04%)	42	2.27(59.52%)
T 1/2 (hr)	41	4.22(17.21%)	41	4.23(18.29%)	42	4.32(19.24%)
Kel (1/hr)	41	0.1693(17.95%)	41	0.1689(17.21%)	42	0.1661(18.56%)

NS: 2x1000/20 mg niacin ER/simvastatin.
NSP: 2 x 1000 mg niacin ER tablets.
ZOC: 2 x 20 mg simvastatin tablets.

Table 9 **Results of statistical analysis for simvastatin relative BA**

Pharmacokinetic Parameter	Comparison	N	LS Mean (test)	N	LS Mean (ref)	LS Mean Ratio (90% Confidence Interval in %)
Cmax (ng/mL)	NS/ZOC	42	11.36	42	9.69	1.1721 (102.95, 133.45)
	NS/NSP+ZOC	42	11.36	42	9.78	1.1609 (101.96, 132.17)
	NSP+ZOC/ZOC	42	9.78	42	9.69	1.0097 (88.76, 114.86)
AUClast (ng.hr/mL)	NS/ZOC	42	41.79	42	34.11	1.2251 (112.36, 133.57)
	NS/NSP+ZOC	42	41.79	42	37.34	1.1191 (102.64, 122.02)
	NSP+ZOC/ZOC	42	37.34	42	34.11	1.0947 (100.48, 119.27)

NS: 2x1000/20 mg niacin ER/simvastatin.
NSP: 2 x 1000 mg niacin ER tablets.
ZOC: 2 x 20 mg simvastatin tablets.

- Results of simvastatin acid relative bioavailability assessment

Mean simvastatin plasma concentration-time profiles by treatments were shown in Figure 6. Simvastatin acid pharmacokinetic parameters and relative BA were summarized in Table 10 and 11. Simvastatin acid Cmax and AUC after Simcor® were 25% and 41% higher than those after Zocor® alone. The higher simvastatin acid AUC (41%) after Simcor® seems to be from the formulation interaction (NS vs. NSP+ZOR; 19% increase) and the drug interaction (NSP+ZOC vs. ZOC; 18% increase).

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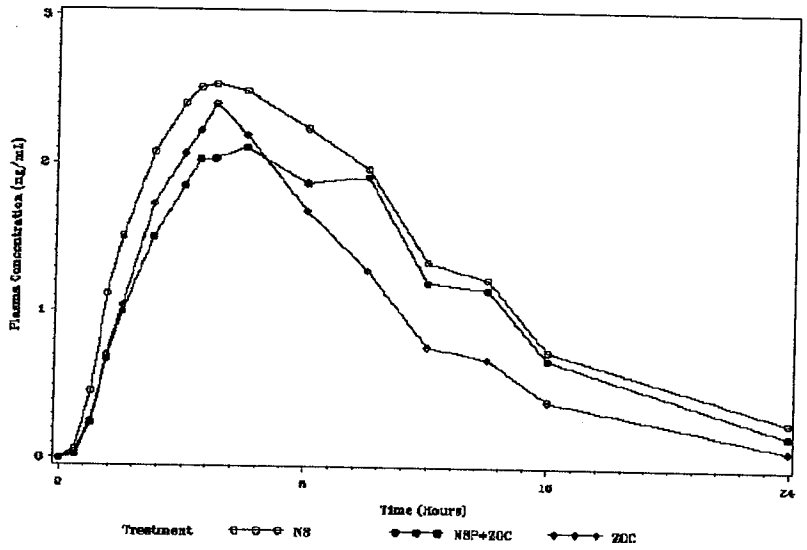

Figure 6 **Mean simvastatin acid plasma concentration-time profiles by treatments**

Table 10 **Mean (%CV) simvastatin acid pharmacokinetic parameters**

Pharmacokinetic Parameter	N	NS (A)	N	ZOC (C)	N	NSP+ZOC (D)
Cmax (ng/mL)	41	3.29(53.05%)	42	2.60(58.75%)	41	2.71(63.97%)
AUClast (ng.hr/mL)	41	30.81(49.06%)	42	21.34(53.65%)	41	25.94(60.81%)
Tmax (hr)	41	6.56(57.92%)	42	5.05(24.73%)	41	5.76(41.89%)
T 1/2 (hr)	34	4.60(34.13%)	38	4.32(26.74%)	36	4.21(26.10%)
Kel (1/hr)	34	0.1655(29.84%)	38	0.1719(27.70%)	36	0.1751(24.19%)

NS: 2x1000/20 mg niacin ER/simvastatin.
NSP: 2 x 1000 mg niacin ER tablets.
ZOC: 2 x 20 mg simvastatin tablets.

Table 11 **Results of statistical analysis for simvastatin acid BA assessment**

Pharmacokinetic Parameter	Comparison	N	LS Mean (test)	N	LS Mean (ref)	LS Mean Ratio (90% Confidance Interval in %)
Cmax (ng/mL)	NS/ZOC	41	2.88	42	2.30	1.2478 (113.39, 137.31)
	NS/NSP+ZOC	41	2.88	41	2.35	1.2217 (110.92, 134.56)
	NSP+ZOC/ZOC	41	2.35	42	2.30	1.0214 (92.90, 112.29)
AUClast (ng.hr/mL)	NS/ZOC	41	26.64	42	18.84	1.4142 (128.67, 155.44)
	NS/NSP-ZOC	41	26.64	41	22.31	1.1944 (108.57, 131.40)
	NSP+ZOC/ZOC	41	22.31	42	18.84	1.1840 (107.83, 130.01)

NS: 2x1000/20 mg niacin ER/simvastatin.
NSP: 2 x 1000 mg niacin ER tablets.
ZOC: 2 x 20 mg simvastatin tablets.

B: 500/20 mg Relative Bioavailability Study (CP-03-012004)

The sponsor conducted a pilot BA study using a single-dose, 3-period, randomized crossover design (n=42 subjects) with the following treatments (Study CP-03-012004):

- **NS-1:** two tablets of 500/20mg niacin ER/simvastatin (Phase 3 formulation)
- **NS-2:** two tablets of 500/20mg niacin ER/simvastatin (a pilot formulation)
- **NSP+ZOC:** two tablets of 500 mg Niaspan® and two tables of 20 mg Zocor®

The study results indicate that dosage forms (500/20mg vs. 1000/20mg) are not equivalent since magnitudes of the formulation interaction (NS vs. NSP+ZOC) for simvastatin and simvastatin acid are different between 500/20mg and 1000/20mg (Table 6,9,11, and 12). Plasma pharmacokinetics of NUA was evaluated without analysis on the total urinary excretion data. Therefore, it is concluded that niacin pharmacokinetics was not fully characterized in this study. Pharmacokinetic parameters for niacin, NUA, simvastatin, and simvastatin acid were summarized in Appendices 5.4.

Table 12 **Relative BA assessment for the Study CP-03-012004**

	Test Treatment	NUA	Simvastatin	Simvastatin Acid
C_{max} (µg/mL)	NS-1	89.7 (77-104)[a]	98.84 (88-111)[a]	113.65 (100-129)[a]
	NS-2	89.7 (77-104)[b]	97.24 (87-109)[b]	112.33 (99-128)[b]
AUC_{last} (µg.hr/mL)	NS-1	90.7 (81-101)[a]	107.98 (100-116)[a]	116.54 (104-130)[a]
	NS-2	94.1 (84-105)[b]	114.39 (106-123)[b]	115.72 (103-129)[b]
NS-1 and NS-2: niacin ER/ simvastatin IR tablet formulations. [a] NS-1 relative to niacin ER (NSP) + simvastatin IR (Zocor, ZOC). [b] NS-2 relative to niacin ER (NSP) + simvastatin IR (Zocor, ZOC). N = 42 for NS-1 and NSP+ZOC; N=41 for NS-2.				
Source: Section 5.3.1.2				

3.2 Analytical Section

3.2.1 What bioanalytical methods are used to assess concentrations?

Plasma niacin, NUA, simvastatin, and simvastatin acid concentrations were measured using an LC/MS/MS. Representative assay validation reports were summarized in Table 13 and it was acceptable.

Table 13 **Plasma assay parameters for niacin, NUA, simvastatin and simvastatin acid and urine assay parameters for niacin, NUA, MNA and 2PY**

Parameter	Niacin	NUA	Simvastatin	Simvastatin Acid
CP-03-012004				
Assay range (ng/mL)	2 to 2000	2 to 2000	0.1 to 50	0.1 to 50
Linearity (correlation coefficient)	>0.99	>0.99	>0.99	>0.99
Precision* (%CV)	1.82 to 10.9	3.79 to 11.1	4.01 to 8.97	10.2 to 13.3
Accuracy* (% difference from theoretical)	-4.92 to 3.32	-5.82 to 3.23	4.52 to 6.27	-0.413 to -1.15
019-03-04-CP				
Assay range (ng/mL)	5 to 2000	5 to 2000	0.1 to 50	0.1 to 50
Linearity (correlation coefficient)	>0.99	>0.99	>0.99	>0.99
Precision* (%CV)	1.92 to 6.24	2.84 to 5.20	2.33 to 7.06	3.65 to 6.93
Accuracy* (% difference from theoretical)	-4.89 to 1.39	-1.96 to 4.54	6.07 to 7.88	1.21 to 6.21

* diluted (niacin and NUA only) and undiluted samples

Source: Section 5.3.1.4, 10-2003 Project TUL, 02-10-04 UUL, Analytical Report Project YXP, Analytical Report Project ZXP

Parameter	Niacin	NUA	MNA	2PY
Assay range (µg/mL)	0.02 to 20	0.2 to 200	0.5 to 250	2.5 to 250
Linearity (correlation coefficient)	>0.990	>0.990	>0.990	>0.990
Precision (%CV)*	1.81 to 4.92	1.56 to 4.95	4.58 to 10.8	3.54 to 8.20
Accuracy (% difference from theoretical)	-0.366 to 3.54	-2.22 to 2.59	-6.48 to 4.75	-2.66 to 1.13

* diluted and undiluted samples

Source: Section 5.3.1.4, Analytical Report Project AYP, Analytical Report Project BYP

3 Page(s) Withheld

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Trade Secret / Confidential

Draft Labeling

Deliberative Process

5 Appendices

5.1 Sponsor's justification to support the 750/20mg Simcor Tablet (e-mail submission on 1/25/08)

Justification to Support the 750/20 mg SIMCOR Tablet Dose Strength

This document provides information requested by the Agency in a January 25, 2008 e-mail from Ms. Kati Johnson (FDA Project Manager), to Dr. David Ross and Mrs. Natalie Tolli (Abbott Laboratories).

FDA Request:

You have proposed three strengths for Simcor 500/20, 750/20, and 1000/20 mg. 1000/20 and 500/20 have been evaluated in relative bioavailability studies as well as in clinical efficacy trials. 750/20 mg, however, has not been evaluated in any of the clinical pharmacology studies. Can you provide a justification for proposing 750/20 mg strength in your NDA

Abbott Response:

- The 750/20 SIMCOR strength was used in the Phase 3, randomized, long-term open label, multicenter clinical study, OCEANS (Protocol 019-02-03-CR, included in the SIMCOR NDA). The 750/20 mg dose strength provides physicians with a dose titration option for the 1500/40 mg dose studied in this protocol

- Relevant clinical pharmacology and dissolution data to support all proposed strengths of the SIMCOR fixed dose combination are summarized below.

  - Niacin Extended-Release: The formulation of the 750 mg niacin extended-release — in SIMCOR 750/20 mg tablets is equivalent to the Niaspan 750 mg strength approved in the Niaspan NDA (20-381). The pharmacokinetics of the Niaspan 750 mg tablet strength have been well-characterized in BA/BE studies submitted to the Niaspan NDA. Comparative bioavailability data from study 019-03-04-CP submitted to the SIMCOR NDA show no impact of the simvastati — on the pharmacokinetics of the niacin extended-release — using 2 x 1000/20 SIMCOR vs 2 x 1000 Niaspan). These results are applicable to lower strengths of SIMCOR tablets (500/20 mg and 750/20 mg strengths).

  - Simvastatin Immediate-Release: In a June 1, 2006 correspondence received from the Agency (included in the SIMCOR NDA) it was agreed that the highest strength (1000/20 mg) of the fixed dose combination product would be used in the 4-way relative BA (interaction) study (19-

03-04-CP). FDA also stated "the two lower strengths 500/20 mg and 750/20 mg should exhibit similar dissolution profiles as the highest strength (1000/20 mg)."

Dissolution data for the three strengths of SIMCOR (submitted in the NDA) show the dissolution rates of simvastatin from the 750/20 mg and 500/20 mg strengths of SIMCOR are faster than the rates shown for 1000/20 mg strength. Module 3, Section 3.2.P.2.2.1.6, *Dissolution Profile Comparisons for Niacin ER/Simvastatin Tablet Strengths*, and Module 2, Section 2.7.1.3.2, *Summary of Biopharmaceutic Studies and Associated Analytical Methods - In Vitro Dissolution*, each summarize findings from Phase I BA/BE Studies CP-03-012004 and 019-03-04-CP and relate the results for the BA/BE studies to the dissolution data. The available data suggest that the differences in simvastatin *in vitro* dissolution between SIMCOR strengths do not translate into differences in *in vivo* performance.

In conclusion, Abbott believes that the available clinical pharmacology data for the 1000/20 mg SIMCOR strength and the available dissolution data as described above support the approval of the 750/20 mg strength of SIMCOR.

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5.2 OCP review for IND 65187 S052

DEPARTMENT OF HEALTH AND HUMAN SERVICES PUBLIC HEALTH SERVICE FOOD AND DRUG ADMINISTRATION	**Clinical Pharmacology & Biopharmaceutics (HFD 870)** **Review for Formal/Informal Consults**	
PIND No.: 65,187	Serial No: 052	SUBMISSION DATE: March 02, 2006
NAME OF DRUG: Niacin/Simvastatin Tablets	NAME OF THE SPONSOR: Kos	
REVIEWER: Wei Qiu, Ph.D.		

TYPE OF SUBMISSION

CLINICAL PHARMACOLOGY/BIOPHARMACEUTICS RELATED ISSUE

☐ PRE-IND	☐ DISSOLUTION/IN-VITRO RELEASE	☐ FINAL PRINTED LABELING
☐ ANIMAL to HUMAN SCALING	☐ BIOAVAILABILITY STUDIES	☐ LABELING REVISION
☐ IN-VITRO METABOLISM	☐ IN-VIVO WAIVER REQUEST	☐ CORRESPONDENCE
☒ PHASE I PROTOCOL	☐ SUPAC RELATED	☐ DRUG ADVERTISING
☐ PHASE II PROTOCOL	☐ CMC RELATED	☐ ADVERSE REACTION REPORT
☐ PHASE III PROTOCOL	☐ PROGRESS REPORT	☐ ANNUAL REPORTS
☐ DOSING REGIMEN CONSULT	☐ SCIENTIFIC INVESTIGATIONS	☐ FAX SUBMISSION
☐ PK/PD- POPPK ISSUES	☒ MEETING PACKAGE (EOP2/Pre-NDA/CMC/Pharmacometrics/Others)	☐ OTHER *(SPECIFY BELOW)*: [ ]
☐ PHASE IV RELATED		

REVIEW ACTION

☐ NAI (No action indicated)	☐ Oral communication with Name: [ ]	☒ Formal Review/Memo (attached)
☐ E-mail comments to:	☐ Comments communicated in meeting/Telecon. see meeting minutes dated: [ ]	☒ See comments below
☐ Medical ☐ Chemist ☐ Pharm-Tox		☐ See submission cover letter
☐ Micro ☐ Pharmacometrics ☐ Others		☐ OTHER *(SPECIFY BELOW)*: [ ]
(Check as appropriate and attach e-mail)		

REVIEW COMMENT(S)

☒ NEED TO BE COMMUNICATED TO THE SPONSOR ☐ HAVE BEEN COMMUNICATED TO THE SPONSOR

COMMENTS/SPECIAL INSTRUCTIONS:

[

List of Specific Questions by Discipline

Discipline: Biopharmaceutics

2. Does FDA agree that the one additional study is adequate to establish the bioequivalence of the original and modified formulations?

Answer: With the information provided by the sponsor, it appears that the Niacin ER —— is unchanged and the BHA is added —— A similar dissolution profiles between the formulations without BHA and with BHA may be used to waiver a BE study.

3. Does FDA agree that these two biopharmaceutics studies together with the SEACOAST and OCEANS studies are adequate to support the filing of the NDA?

Answer: From biopharm perspective, these issues need to be considered: (1). It is understood that the there was an agreement between the sponsor the agency that the highest strength (1000/20) of the combination product would be used in the 4-way relative bioavailability (interaction) study. One 1000/20 NS tablet is recommended for this study. The modified formulation with BHA can be used in this study. (2). The two lower strengths 500/20 and 750/20 should exhibit similar dissolution profiles as the highest strength.

]

SIGNATURE OF REVIEWER: _____	Date _____
SIGNATURE OF TEAM LEADER: _____	Date _____

Background:

Niacin extended-release and simvastatin (NS) tablets are a fixed-dose combination product of extended-release niacin (Niaspan®) and simvastatin, intended for use in the treatment of primary hypercholesterolemia and mixed dyslipidemia.

Three NS combination tablet strengths are under development: 500/20, 750/20, and 1000/20 (mg of niacin/mg of simvastatin). Patients may receive daily doses up to 2000/40 of NS.

On March 02, 2006 the sponsor Kos submitted an IND for NS tablets to discuss a formulation change to include an ——— and a bridging bioequivalence study to compare the revised and original formulation. Due to ———— ———————————————————————————— , Kos is evaluating the addition of a ——— butylated hydroxyanisole, BHA) to the tablet formulations. To link this modified formulation to the original, Kos proposed to conduct a two-way, two-treatment single-dose bioequivalence study comparing the nonBHA-containing formulation used in the clinical trials and the formulations containing BHA proposed for commercialization. The sponsor would like concurrence from FDA that the proposed bioequivalence study is the only additional study required.

The proposed BE study was to determine the bioequivalence of a reformulated 1000/20 mg extended-release niacin (ER)/simvastatin immediate-release (IR) combination tablet (Test) versus the current 1000/20 mg niacin ER/simvastatin IR investigational NS tablet (reference) administered at a dose of 2000/40 mg.

The study has randomized, single-dose, replicate, crossover design, with two treatments and four periods with minimum 10 day washout between each treatment. Each subject receives the Test treatment on two separate occasions and the Reference treatment on two separate occasions. Each dose will be administered after a low-fat snack.

Blood samples for PK determination will be collected pre-dose and at 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 6, 8, 10, 12, 14, 16, and 24 hours after dosing (16 samples/treatment). Niacin, nicotinuricacid (NUA), simvastatin, and simvastatin acid concentrations will be assayed in all plasma samples by validated LC/MS/MS methods. PK urine samples will be collected at interval collections for -24 to -18, -18 to -12, -12 to -6, -6 to 0 hours (i.e., prior to dosing), and then 0 to 6, 6 to 12, 12 to 18, 18 to 24, 24 to 48, 48 to 72, and 72 to 96 hours after dosing. Niacin, NUA, N-methylnicotinamide (MNA), and N-methyl-2-pyridone-5-carboxamide (2PY) will be assayed in all urine samples by validated LC/MS/MS methods.

A total of 44 healthy 40 to 70 year-of-age inclusive subjects will be included. The following PK parameters will be determined: Niacin: plasma Cmax for NUA and total amount recovered in urine as niacin and metabolites (NUA, MNA, and 2PY); simvastatin: plasma Cmax and AUClast for simvastatin and simvastatin acid.

Plasma Cmax of NUA and total urinary excretion of niacin and metabolites including NUA, MNA and 2PY has been used to characterize the niacin absorption rate and extent, respectively.

Statistical methods: construct 90% confidence interval for the Test/Reference (Treatment A/Treatment B) ratios for the natural log-transformed simvastatin, simvastatin acid, NUA Cmax and total amount recovered in urine as niacin and metabolites to determine BE.

List of Specific Questions by Discipline

Discipline: Biopharmaceutics

Due to the inclusion of [redacted] in the modified formulations proposed for commercialization, Kos believes a single "bridging" bioequivalence study using NS 1000/20 tablets (highest tablet strength) with and without BHA in the coated tablets, is required. The draft study protocol is provided in Attachment 2.

This bioequivalence study is in addition to a 4-way relative bioavailability (interaction) study that was previously agreed to with the Agency (refer to Attachment 1, section 3, for a more detailed description). The design of the 4-way study will change only in that NS 1000/20 tablets with BHA will be used instead of the original formulation that does not contain BHA.

2. Does FDA agree that the one additional study is adequate to establish the bioequivalence of the original and modified formulations?

Answer: With the information provided by the sponsor, it appears that the Niacin ER [redacted] is unchanged and the BHA is added to th[redacted] A similar dissolution profiles between the formulations without BHA and with BHA may be used to waiver a BE study.

3. Does FDA agree that these two biopharmaceutics studies together with the SEACOAST and OCEANS studies are adequate to support the filing of the NDA?

Answer: From biopharm perspective, these issues need to be considered: (1). It is understood that the there was an agreement between the sponsor the agency that the highest strength (1000/20) of the combination product would be used in the 4-way relative bioavailability (interaction) study. However, one 1000/20 NS tablet is recommended for this study. The modified formulation with BHA can be used in this study. (2). the two lower strengths 500/20 and 750/20 should exhibit similar dissolution profiles as the highest strength.

Appendix: 4-way study protocol

5.3 Individual Study Synopsis (Study 019-03-04-CP)

2.7.6.1 BIOAVAILABILITY STUDY SYNOPSES

2.7.6.1.1 Study 019-03-04-CP

Sponsor: **Kos Life Sciences, Inc.**	**Individual Study Table Referring to Part of the Dossier**	**(For National Authority Use only)**
Name of Finished Product: **Niacin ER/ Simvastatin Tablets**	**Volume:**	
Name of Active Ingredient: **Niacin, USP; Simvastatin, USP**	**Page:**	
Study Title: The Comparative Bioavailability of a Niacin and Simvastatin Combination Versus Niaspan® and Zocor®		
Investigator(s) and Study Center(s): Maria J. Gutierrez, MD, Comprehensive PHASE ONE, Ft Lauderdale, FL		
Publication (reference): NA		
Studied Period: 25 May 2006 (first subject enrolled) to 30 June 2006 (last subject completed)		
Study Phase: Phase I		
Objective: To compare the bioavailability (BA) of niacin and simvastatin from a combination tablet relative to administration of Niaspan alone, Zocor alone and the co-administration of Niaspan and Zocor		
Methodology: Randomized, single-center, open-label, single-dose, four-way crossover design in healthy volunteers, with four sequences and four periods, lasting approximately 6 days each with a minimum 10 days washout between each treatment. Every subject received each of the following four treatments – one treatment during each of the four periods: NS: 2000/40 mg niacin/simvastatin (2 tablets each containing 1000 mg niacin ER and 20 mg simvastatin) NSP: 2000 mg niacin ER (2 x 1000 mg Niaspan tablets) ZOC: 40 mg simvastatin (2 x 20 mg Zocor tablets) NSP + ZOC: 2000 mg niacin ER (2 x 1000 mg Niaspan tablets) and 40 mg simvastatin (2 x 20 mg Zocor tablets) administered together.		

Sponsor: Kos Life Sciences, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Niacin ER/ Simvastatin Tablets	Volume:	
Name of Active Ingredient: Niacin, USP; Simvastatin, USP	Page:	

PK Blood Samples: Pre-dose (within 30 min of the dose of the study drug) and 0.5, 1, 1.5, 2, 3, 4, 4.5, 5, 6, 8, 10, 12, 14, 16, and 24 hrs after dosing (16 samples/treatment); all samples were collected in vacutainers with sodium heparin. Niacin, nicotinuricacid (NUA), simvastatin, and simvastatin acid concentrations were assayed by validated LC/MS/MS methods.

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

Number of Subjects (Planned and Analyzed):

44 subjects were planned and 44 subjects were analyzed for PK and safety.

Diagnosis and Main Criteria for Inclusion:

Subjects enrolled in the study were healthy men and women, 40 to 70 yrs-of-age inclusive, who were not tobacco users for at least 120 days prior to receiving the first dose of study medication, and without any clinically significant (CS) abnormalities at the screening visit and at the first study period admission visit. Women included in the study had to be at least 3 yrs post-menopausal or had either a total hysterectomy, bilateral oophorectomy, or tubal ligation, and were therefore not of child-bearing potential. Women younger than 60 yrs-of-age had to have negative pregnancy tests at both the screening visit and each study period admission visit. The acceptable weight range for men was between 154 and 211 pounds and for women was between 130 and 198 pounds. Weight also had to be within the range shown for height and frame size indicated in the protocol at the screening visit.

Test Product, Dose and Mode of Administration, Lot Number:

Treatment NS: 2 x Niacin/Simvastatin 1000/20 mg reformulated NS tablets (BHA added [redacted] each containing 1000 mg niacin ER and 20 mg simvastatin IR; Lot number 137S019.

Duration of Treatment: Dosing in the first study period started within 21 days of screening. Subjects were sequestered in the clinic for four study periods lasting approximately six days each with a minimum 10-day washout period between each treatment.

Sponsor: Kos Life Sciences, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Niacin ER/ Simvastatin Tablets	Volume:	
Name of Active Ingredient: Niacin, USP; Simvastatin, USP	Page:	

Reference Therapy, Dose and Mode of Administration, Lot Number:

NSP: 2000 mg niacin ER (2 x 1000 mg niacin ER tablets). These niacin ER tablets were the [redacted] to produce the NS tablets. They are equivalent to Niaspan tablets and is hence referred to as Niaspan tablets in the study. ZOC: 40 mg simvastatin (2 x 20 mg Zocor tablets)
NSP + ZOC: 2000 mg niacin ER (2 x 1000 mg Niaspan tablets) and 40 mg simvastatin (2 x 20 mg Zocor tablets) administered in combination
Lot number for NSP was 122S019 and for ZOC was F0886

Criteria for Evaluation:

Pharmacokinetics:
Pharmacokinetic data were analyzed from all subjects who completed at least one treatment period. Niacin BA was compared using NUA Cmax, and total recovery of niacin and its three metabolites in urine (NUA, MNA, 2-PY) while simvastatin BA was compared using simvastatin and simvastatin acid C_{max} and AUC_{last}.

Safety:
Adverse event data were summarized from all subjects who received at least one dose of study medication.

Statistical Methods:

Least Square (LS) mean ratios and the associated 90% confidence intervals were constructed for the natural log-transformed PK parameters. The primary parameters evaluated included NUA C_{max}, and total recovery of niacin and its three metabolites in urine; simvastatin and simvastatin acid C_{max} and AUC_{last}. NUA AUC_{last} was used as a supportive parameter for niacin BA. The following ratios were determined:
For niacin: NSP + ZOC over NSP; NS over NSP; NS over NSP + ZOC
For simvastatin: NSP + ZOC over ZOC; NS over ZOC; NS over NSP + ZOC
The 90% CI for the ratios measuring relative bioavailability should lie within the acceptance interval of 0.80 to 1.25.

Demographics and adverse events were summarized.

Pharmacokinetic Variables:

The following PK parameters were calculated:
For niacin, NUA, simvastatin and simvastatin acid in plasma: the maximum plasma concentration (C_{max}), time at which C_{max} occurs (T_{max}), and area under the concentrationtime profile from time 0 to the last measurable concentration (AUC_{last}). For

Sponsor: Kos Life Sciences, Inc.	Individual Study Table Referring to Part of the Dossier	(For National Authority Use only)
Name of Finished Product: Niacin ER/ Simvastatin Tablets	Volume:	
Name of Active Ingredient: Niacin, USP; Simvastatin, USP	Page:	
simvastatin and simvastatin acid only, terminal elimination rate constant (λ_z), and terminal elimination half-life ($T_{1/2}$) were calculated For niacin and metabolites (NUA, MNA and 2PY) in urine the fraction excreted in urine during the 96 hour collection corrected for baseline recovery and molecular weight ($\%Fe_{(0\text{-}96h)Corr}$) and recovery for all four analytes combined (i.e., total recovery) as percent of niacin dose ($\%Fe_{Total\ (0\text{-}96h)}$)		
Safety: Adverse events were summarized.		

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Summary of Results

Forty-four adult subjects, 21 males and 23 of females, were enrolled in the study. All subjects completed the study, with the exception subject 0004 who completed 3 of 4 periods and subjects 0039 and 0040 who completed 1 of 4 periods.

Pharmacokinetic:

Niacin:

The primary variables designed to evaluate Niacin rate and extent of absorption were NUA C_{max} and total urinary recovery of niacin and its three major metabolites (NUA, MNA, and 2PY) respectively. As shown in Table 1, the 90% CI for the natural-log transformed ratios of these primary BA variables were within the 80-125% range for all comparisons indicating comparable bioavailability between treatments. Mean T_{max} values for NUA was approximately 5 hours for all the 3 treatments

Table 1: Summary of NUA plasma parameters and total urinary recovery of niacin and metabolites

PK Parameter	Treatment	N	Arithmetic Mean (%CV)	Comparison	LS Mean Ratio (90% Confidence Interval)
NUA C_{max}[a] (ng/mL)	NS	42	3493.8 (52)	NS/NSP	0.96 (88.16, 104.22)
	NSP	41	3501.0 (44)	NS/NSP+ZOC	1.08 (99.84, 117.88)
	NSP+ZOC	41	3254.1 (56)	NSP+ZOC/NSP	0.88 (81.26, 96.08)
NUA AUC_{last}[c] (ng.hr/mL)	NS	42	16998.6 (67)	NS/NSP	0.97 (88.89, 106.30)
	NSP	41	16512.4 (56)	NS/NSP+ZOC	1.06 (96.95, 115.77)
	NSP+ZOC	41	16142.4 (70)	NSP+ZOC/NSP	0.92 (83.90, 100.33)
% Fe(0-96h)Total[a, b]	NS	41	54.1 (22)	NS/NSP	0.99 (93.37, 105.09)
	NSP	40	54.5 (19)	NS/NSP+ZOC	1.01 (94.99, 106.75)
	NSP+ZOC	41	53.6 (23)	NSP+ZOC/NSP	0.98 (92.53, 104.23)

[a] Primary parameters for niacin BA assessment; [b] Urinary recovery of niacin, NUA, MNA and 2PY combined
[c] Supportive parameters for niacin BA assessment

Simvastatin:

As indicated in Table 2, the rate (C_{max}) and extent (AUC_{last}) of simvastatin exposure for all of the planned comparisons, had ratios greater than 100% with the exception of C_{max} for the NSP+ZOC versus ZOC comparison, which had a ratio of ~100%. The greatest increase in rate (17%) and extent (23%) were seen with NS relative to ZOC. The NS versus NSP + ZOC comparison indicated a 16% increase in rate and a 12% increase in extent of simvastatin relative exposure. The 90% CI for the LS mean ratios for NSP+ZOC over ZOC were within the 80 to 125% acceptance interval for both Cmax and AUC_{last}. The upper bound for the 90% CI for the LS mean ratio of NS over ZOC was higher than the 80 to 125% acceptance interval for both Cmax and AUClast. The upper bound for the 90% CI

for the LS mean C_{max} ratio for NS over NSP+ZOC was also higher than the 80 to 125% acceptance interval, though the 90% CI for the AUC_{last} ratio was within the 80 to 125% interval for both C_{max} and AUC_{last}. These results suggest that the BA of NS was higher than ZOC but NSP+ZOC showed comparable BA to ZOC. The mean T_{max} for simvastatin was around 2 hours, and the mean $t_{1/2}$ around 4.25 hours for all three treatments.

Table 2: Summary of simvastatin plasma parameters

PK Parameter	Treatment	N	Arithmetic Mean (%CV)	Comparison	LS Mean Ratio (90% Confidence Interval)
C_{max} (ng/mL)	NS	42	13.28 (61)	NS/ZOC	1.17 (102.95, 133.45)
	ZOC	42	10.94 (59)	NS/NSP+ZOC	1.16 (101.96, 132.17)
	NSP+ZOC	42	11.05 (55)	NSP+ZOC/ZOC	1.01 (88.76, 114.86)
AUC_{last} (ng.hr/mL)	NS	42	49.02 (69)	NS/ZOC	1.23 (112.36, 133.57)
	ZOC	42	37.70 (58)	NS/NSP+ZOC	1.12 (102.64, 122.02)
	NSP+ZOC	42	40.10 (44)	NSP+ZOC/ZOC	1.09 (100.48, 119.27)

As indicated in the Table 3, the rate (C_{max}) and extent (AUC_{last}) of simvastatin acid exposure for all of the planned comparisons had LS mean ratios greater than 100% and the upper bound of the 90% CI outside the acceptable 80 to 125% interval with the exception of C_{max} for the NSP+ZOC versus ZOC comparison, which had a ratio of ~100% and CI within the 80 to 125% interval. The greatest increase in rate and extent were seen with NS as compared to ZOC with 25% and 41% respectively. The NS versus NSP + ZOC comparison indicated a 22% increase in rate and a 19% increase in extent of simvastatin relative bioavailability. These results indicate that the BA of simvastatin acid was higher from NS and NSP+ZOC as compared to ZOC. The mean T_{max} for simvastatin acid occurred later with the NS treatment (6.56 hours) as compared to ZOC (5.05 hours) and NSP+ZOC (5.76 hours). The mean $t_{1/2}$ for all three treatments was between 4 and 5 hours.

Table 3: Summary of simvastatin acid plasma parameters

PK Parameter	Treatment	N	Arithmetic Mean (%CV)	Comparison	LS Mean Ratio (90% Confidence Interval)
C_{max} (ng/mL)	NS	41	3.29 (53)	NS/ZOC	1.25 (113.39, 137.31)
	ZOC	42	2.60 (59)	NS/NSP+ZOC	1.22 (110.92, 134.56)
	NSP+ZOC	41	2.71(64)	NSP+ZOC/ZOC	1.02 (92.90, 112.29)
AUC_{last} (ng.hr/mL)	NS	41	30.81 (49)	NS/ZOC	1.41 (128.67, 155.44)
	ZOC	42	21.34 (54)	NS/NSP+ZOC	1.19 (108.57, 131.40)
	NSP+ZOC	41	25.94 (61)	NSP+ZOC/ZOC	1.18 (107.83, 130.01)

Safety:

Forty two (95%) subjects reported at least one adverse event. Thirty eight (88.4%) out of the 43 subjects dosed with NS reported at least one adverse event while 34 (81.0%), 4 (9.5%) and 33 (78.6%) out of 42 subjects dosed with NSP, ZOC and NSP + ZOC respectively reported at least one adverse event.

There were a total of 148 adverse events reported over the four treatment periods. All the reported adverse events were mild in intensity. One hundred twelve (75.7%) adverse events were classified as probably related to the study medications. Twenty three (15.5%) adverse events were classified as possibly related to the study medications. The remaining 13 (8.8%) adverse events were classified as unrelated to the study medications.

The most common AE was flushing, experienced by 37 (86.0%) subjects following NS Treatment, by 32 (76.2%) subjects following NSP Treatment, 3 (7.1%) subjects following ZOC treatment and 32 (76.2%) subjects following NSP+ZOC Treatment. Headache was the next most common AE, reported by four (9.3%) subjects following NS Treatment, two (4.8%) subjects following NSP Treatment, one (2.4%) subject following ZOC Treatment and four (9.5%) subjects following NSP+ZOC Treatment. The third most common AE was nausea reported by one (2.3%) subject following NS Treatment, one (2.4%) subject following NSP Treatment and two (4.8%) subjects following NSP+ZOC Treatment.

Three subjects discontinued the study due to AEs. Two of the three AE's that led to discontinuations were not related to the study treatments per the PI.

CONCLUSIONS

Pharmacokinetic Conclusions:

- The rate of niacin absorption as measured by NUA C_{max} and the extent of niacin absorption as measured by the total recovery of niacin and three of its metabolites (NUA, MNA and 2-PY) in urine were comparable across the three treatments NS, Niaspan and Niaspan + Zocor as the 90% CI of the least square mean ratios for these comparisons were within the 80 to 125% acceptance interval.

- The co-administration of Niaspan and Zocor showed comparable rate of exposure but a 9% and 18% higher extent of exposure for simvastatin and simvastatin acid respectively when compared to Zocor administration alone. While 90% CI of the ratios for the rate and extent of Simvastatin exposure were within the 80 to 125% acceptance interval the 90% CI for simvastatin acid extent of exposure was outside the 80 to 125% indicating that simvastatin bioavailability was comparable but simvastatin acid exposure from Niaspan + Zocor administration was higher than for Zocor administered alone.

- The NS formulation showed 17% and 25% higher rate of exposure and 23% and 41% higher extent of exposure for simvastatin and simvastatin acid respectively as

compared to Zocor. The upper bound of the 90% CI of the ratios for the comparisons were higher than the 80-125% acceptance interval, indicating higher bioavailability of simvastatin and simvastatin acid from the NS formulation as compared to Zocor.

- The NS formulation showed 16% and 22% higher rate of exposure and 12% and 19% higher extent of exposure for simvastatin and simvastatin acid respectively as compared to Niaspan + Zocor. The upper bound of the 90% CI of the ratios for the comparisons were higher than the 80 to 125% acceptance interval for all comparisons except simvastatin AUC_{last}, indicating higher bioavailability of simvastatin and simvastatin acid from the NS formulation as compared to Niaspan + Zocor.

- In summary, it appears that while the bioavailability of niacin is unaffected in combination with simvastatin, simvastatin and simvastatin acid exposure are higher from the NS formulation. This is explained by a small interaction between niacin and simvastatin (NSP + ZOC versus ZOC) and higher simvastatin bioavailability from the NS formulation.

- The small increase in simvastatin and simvastatin acid exposure from NS is not clinically significant.

Safety Conclusions:

- The study treatments were well tolerated. Flushing was the most common AE reported. Overall, the adverse events were mild and resolved by the completion of the study or within the 30-day follow-up window. No SAEs were reported. There were three discontinuations due to AE's.

Final Date: 4 December 2006

Prepared in: Microsoft Word 2000

5.4 Niacin, NUA, simvastatin, and simvastatin acid pharmacokinetic parameters (Study CP-03-012004)

		Plasma Niacin			Statistics	
		Mean	SD	% CV	Ratio(%)	90% CI
C_{max} (µg/mL)						
	ERN+ZOC	1.434	2.469	172.3		
	N/S-1	0.734	0.959	130.8	69.9[a]	50-98
	N/S-2	0.832	1.217	146.3	76.3[a]	55-107
AUC_{last} (µg*hr/mL)						
	ERN+ZOC	2.518	4.350	172.8		
	N/S-1	1.548	1.860	120.2	81.9[a]	62-108
	N/S-2	1.728	2.654	153.6	83.8[a]	63-111
T_{max} (hr)						
	ERN+ZOC	3.976	1.581	39.8		
	N/S-1	4.643	1.782	38.4	116.8[b]	103-130
	N/S-2	4.073	1.856	45.6	101.5[b]	88-115[c]
AUC_{inf} (µg*hr/mL)						
	ERN+ZOC	2.573	4.391	170.6		
	N/S-1	1.392	1.295	93.0	NC	NC
	N/S-2	1.827	2.702	147.9	NC	NC
k (1/hr)						
	ERN+ZOC	0.734	0.705	96.1		
	N/S-1	0.604	0.609	100.7	NC	NC
	N/S-2	0.640	0.546	85.4	NC	NC
$t_{1/2}$ (hr)						
	ERN+ZOC	1.642	1.081	65.8		
	N/S-1	2.123	1.416	66.7	NC	NC
	N/S-2	2.345	2.159	92.1	NC	NC

Each treatment consists of 1000 mg niacin.
N = 42 except for N/S-2 where N = 41
[a] Ratio of the least square means of the natural-log transformed niacin Cmax and $AUC_{0\text{-}last}$.
[b] Ratio of the least square means of the non-transformed niacin Tmax.
[c] Suggests bioequivalence (i.e., 90% CI within 80-120% for the not-transformed niacin Tmax).
NC = not calculated
Data Source: Appendices B, C, and G

		Plasma NUA			Statistics	
		Mean	SD	% CV	Ratio(%)	90% CI
C_{max} (μg/mL)						
	ERN+ZOC	1.445	0.860	59.5		
	N/S-1	1.230	0.741	60.2	89.7[a]	77-104
	N/S-2	1.341	0.809	60.3	89.7[a]	77-104
AUC_{last} (μg*hr/mL)						
	ERN+ZOC	5.598	3.155	56.4		
	N/S-1	5.121	3.268	63.8	90.7[a]	81-101[c]
	N/S-2	5.474	3.017	55.1	94.1[a]	84-105[c]
T_{max} (hr)						
	ERN+ZOC	4.464	1.359	30.4		
	N/S-1	5.095	1.620	31.8	114.1[b]	104-124
	N/S-2	4.110	1.519	37.0	91.5[b]	81-102[d]
AUC_{inf} (μg*hr/mL)						
	ERN+ZOC	5.620	3.164	56.3		
	N/S-1	5.145	3.281	63.8	NC	NC
	N/S-2	5.498	3.032	55.1	NC	NC
k (1/hr)						
	ERN+ZOC	0.238	0.090	37.7		
	N/S-1	0.246	0.091	37.0	NC	NC
	N/S-2	0.232	0.086	36.9	NC	NC
$t_{1/2}$ (hr)						
	ERN+ZOC	3.226	0.916	28.4		
	N/S-1	3.116	0.879	28.2	NC	NC
	N/S-2	3.306	0.943	28.5	NC	NC

Each treatment consists of 1000 mg niacin.
N = 42 except for N/S-2 where N = 41
[a] Ratio of the least square means of the natural-log transformed NUA Cmax and $AUC_{0\text{-last}}$.
[b] Ratio of the least square means of the non-transformed NUA Tmax.
[c] Suggests bioequivalence (i.e., 90% CI within 80-125% for the natural-log transformed NUA $AUC_{0\text{-last}}$).
[d] Suggests bioequivalence (i.e., 90% CI within 80-120% for the not-transformed NUA Tmax).
NC = not calculated
Data Source: Appendices B, C, and G

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		Plasma Simvastatin			Statistics	
		Mean	SD	% CV	Ratio(%)	90% CI
C_{max} (ng/mL)						
	ERN+ZOC	12.305	6.840	55.6		
	N/S-1	12.273	7.319	59.6	98.84[a]	88-111[c]
	N/S-2	11.928	6.632	55.6	97.24[a]	87-109[c]
AUC_{last} (ng*hr/mL)						
	ERN+ZOC	40.888	22.178	54.2		
	N/S-1	42.622	18.719	43.9	107.98[a]	100-116[c]
	N/S-2	47.400	29.235	61.7	114.39[a]	106-123[c]
T_{max} (hr)						
	ERN+ZOC	2.060	0.813	39.5		
	N/S-1	1.881	1.041	55.3	91.33[b]	77-105
	N/S-2	1.524	0.836	54.9	73.74[b]	60-88
AUC_{inf} (ng*hr/mL)						
	ERN+ZOC	42.398	22.440	52.9		
	N/S-1	44.503	19.134	43	NC	NC
	N/S-2	49.545	29.87	60.3	NC	NC
k (1/hr)						
	ERN+ZOC	0.155	0.040	26.0		
	N/S-1	0.157	0.047	29.8	NC	NC
	N/S-2	0.158	0.047	29.6	NC	NC
$t_{1/2}$ (hr)						
	ERN+ZOC	4.843	1.567	32.4		
	N/S-1	4.872	1.727	35.5	NC	NC
	N/S-2	4.916	2.119	43.1	NC	NC

Each treatment consists of 40 mg simvastatin.
N = 42 except for N/S-2 where N = 41
[a] Ratio of the least square means of the natural-log transformed Simvastatin Cmax and $AUC_{0\text{-last}}$.
[b] Ratio of the least square means of the non-transformed Simvastatin Tmax.
[c] Suggests bioequivalence (i.e., 90% CI within 80-125% for the natural-log transformed Simvastatin Cmax and $AUC_{0\text{-last}}$).
NC = not calculated
Data Source: Appendices B, C, and G

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		Plasma Simvastatin Acid			Statistics	
		Mean	SD	% CV	Ratio(%)	90% CI
C_{max} (ng/mL)						
	ERN+ZOC	2.977	2.841	95.4		
	N/S-1	3.469	3.176	91.6	113.65[a]	100-129
	N/S-2	3.444	2.751	79.9	112.33[a]	99-128
AUC_{last} (ng*hr/mL)						
	ERN+ZOC	27.272	24.278	89.0		
	N/S-1	31.209	25.922	83.1	116.54[a]	104-130
	N/S-2	31.699	23.234	73.3	115.72[a]	103-129
T_{max} (hr)						
	ERN+ZOC	4.929	1.587	32.2		
	N/S-1	5.321	2.424	45.6	116.77	103-130
	N/S-2	4.841	1.998	41.3	101.45	88-115[c]
AUC_{inf} (ng*hr/mL)						
	ERN+ZOC	29.415	24.214	82.3		
	N/S-1	33.925	26.913	79.3	NC	NC
	N/S-2	34.452	24.202	70.3	NC	NC
k (1/hr)						
	ERN+ZOC	0.162	0.050	30.8		
	N/S-1	0.158	0.049	31.2	NC	NC
	N/S-2	0.145	0.047	32.7	NC	NC
$t_{1/2}$ (hr)						
	ERN+ZOC	4.920	2.676	54.4		
	N/S-1	5.035	2.308	45.8	NC	NC
	N/S-2	5.475	2.615	47.8	NC	NC

Each treatment consists of 40 mg simvastatin.
N = 42 except for N/S-2 where N = 41
[a] Ratio of the least square means of the natural-log transformed Simvastatin acid Cmax and $AUC_{0\text{-last}}$.
[b] Ratio of the least square means of the non-transformed Simvastatin acid Tmax.
[c] Suggests bioequivalence (i.e., 90% CI within 80-120% for the non-transformed Simvastatin acid Tmax.
NC = not calculated
Data Source: Appendices B, C, and G

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/s/

Sang Chung
2/15/2008 03:39:38 PM
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Sally Choe
2/15/2008 03:40:35 PM
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1/23/08

Office of Clinical Pharmacology
New Drug Application Filing and Review Form

General Information About the Submission

	Information		Information
NDA Number	22-078	Brand Name	Simcor
OCP Division	DCP II	Generic Name	Niacin ER/simvastatin
Medical Division	DMEP	Drug Class	
OCP Reviewer	Sang M. Chung, Ph.D.	Indication(s)	Treatment of primary hypercholesterolemia, mixed dyslipidemia, and hypertriglyceridemia
OCP Pharmacometrics Reviewer	N/A	Dosage Form	Tablet; 500/20, 750/20, 1000/20 (mg/mg)
OCP Team Leader	Sally Choe, Ph.D. (Acting)	Dosing Regimen	500/20 mg/day through 2000/40mg/day
Date of Submission	March 2, 2005	Route of Administration	Oral
Estimated Due Date of OCP Review	1/11/08	Sponsor	Abbott
PDUFA Due Date		Priority Classification	S
Division Due Date			

Clin. Pharm. and Biopharm. Information

	"X" if included at filing	Number of studies submitted	Number of studies reviewed	Critical Comments If any
STUDY TYPE				
Table of Contents present and sufficient to locate reports, tables, data, etc.	X			
Tabular Listing of All Human Studies	X			
HPK Summary	X			
Labeling	X			
Reference Bioanalytical and Analytical Methods	X			
I. Clinical Pharmacology				
Mass balance:				
Isozyme characterization:				
Blood/plasma ratio:				
Plasma protein binding:				
Pharmacokinetics (e.g., Phase I) -				
Healthy Volunteers-				
single dose:				
multiple dose:				
Patients-				
single dose:				
multiple dose:				
Dose proportionality -				
fasting / non-fasting single dose:				
fasting / non-fasting multiple dose:				
Drug-drug interaction studies -				
In-vivo effects on primary drug:				
In-vivo effects of primary drug:				
In-vitro:				
Subpopulation studies -				
ethnicity:				
gender:				
pediatrics:				
geriatrics:				
renal impairment:				
hepatic impairment:				

PD:				
Phase 2:				
Phase 3:				
PK/PD:				
Phase 1 and/or 2, proof of concept:				
Phase 3 clinical trial:				
Population Analyses -				
Data rich:				
Data sparse:				
II. Biopharmaceutics	X	3		
Absolute bioavailability:				
Relative bioavailability -	X	1		
solution as reference:				
alternate formulation as reference:				
Bioequivalence studies -	X	2		
traditional design; single / multi dose:				
replicate design; single / multi dose:				
Food-drug interaction studies:				
Dissolution:				
(IVIVC):				
Bio-wavier request based on BCS				
BCS class				
III. Other CPB Studies				
Genotype/phenotype studies:				
Chronopharmacokinetics				
Pediatric development plan				
Literature References				
Total Number of Studies		3		

Filability		
	"X" if yes	Comments
Application filable ?	X	
Submission in brief	This submission is a 505(b)(2) application referencing data from NDA 20-381 (Niaspan® for niacin ER) and NDA 19-776 (Zocor® for Simvastatin). The sponsor conducted total 5 clinical studies and study design and treatments were summarized in Table 1. Pivotal pharmacokinetics of niacin and simvastatin were characterized after Simcor® administration (019-03-04-CP, Table 1). Niacin BA after Simcor® administration was comparable to that after niacin alone (Treatment C) or Treatment D. Simvastatin and Simvastatin acid BA after Simcor® administration was higher than that after Treatment B or Treatment D (Table 2). Study CP-03-012004 was a pilot BA study to evaluate early combination formulations. Pharmacokinetic analyses were not conducted for Study 019-04-05-CP since the change in the to-be-marketed formulation (i.e., addition of butylated hydroxyanisole ———) was regarded as a biowaiver according to the EOP2 meeting minute. For relative BA assessment, the following four surrogate PK endpoints were estimated: • Cmax of NUA, one of niacin metabolites, for the rate of niacin absorption • Urinary excretion of metabolites and niacin for the extent of niacin absorption • Cmax of simvastatin and simvastatin acid for the simvastatin rate of absorption and AUC of simvastatin and simvastatin acid for the extent of absorption.	

Table 1 Summary of treatments for clinical studies

Study	Number of Subjects Randomized	Study design	Treatment regimen[a]
Phase 1			
CP-03-012004	42	Single-dose, randomized, single-center, open-label, 3-way cross-over study in healthy, non-smoking men and women	Treatment on 3 separate occasions, at least 7 days apart, with 1 of 3 treatments: 2 tablets each of 1 of 2 different formulations of niacin ER/simvastatin 500/20 tablets *or* 2 niacin ER 500 mg tablets plus 2 simvastatin 20 mg tablets
019-03-04-CP	44	Single-dose, randomized, single-center, open-label, 4-way crossover study in healthy, non-smoking men and women	Treatment on 4 separate occasions with at least 10 days between dosing. **Treatment A:** 2 NS 1000/20 tablets **Treatment B:** 2 Niacin ER 1000 mg tablets **Treatment C:** 2 simvastatin 20 mg tablets **Treatment D:** 2 Niacin ER 1000 mg and 2 simvastatin 20 mg tablets
019-04-05-CP	44	Single-dose, randomized, single-center, open-label, replicate (ABAB or BABA), 4-period, 2-treatment, crossover study in healthy, non-smoking men and women	Treatment with the same dose of NS on 4 separate occasions with at least 10 days between dosing. **Treatment A:** 2 NS 1000/20 tablets (reformulated with BHA) **Treatment B:** 2 NS 1000/20 tablets (without BHA)
Phase 3			
SEACOAST	662	24-week, multinational, multicenter, randomized, double-blind, parallel-arm, active-controlled study	Treatment for 24 weeks in 1 of the following dose groups. **Dose Group A:** daily doses of NS 1000/20, NS 2000/20, or 20 mg simvastatin **Dose Group B:** daily doses of NS 1000/40, NS 2000/40, or 80 mg simvastatin
OCEANS	520	52-week, multicenter, randomized, open-label, parallel-group, uncontrolled study	Treatment for up to 52 weeks with NS daily, in 2 different titration regimens, to a maximum dose of 2000/40.

[a] Niacin ER simvastatin (NS) doses expressed as mg niacin ER mg simvastatin.

BHA: butylated hydroxyl anisole; ER: extended release

Table 2 relative BA assessment of niacin, simvastatin, and simvastatin acid

Parameter (units)	Treatment Comparisons	N	NUA*	Simvastatin*	Simvastatin acid*
C_{max} (ng/mL)	NS/NSP or NS/ZOC†	42	0.96 (88.16, 104.22)	1.17 (102.95, 133.45)	1.25 (113.39, 137.31)
	NS/NSP+ZOC	41	1.08 (99.84, 117.88)	1.16 (101.96, 132.17)	1.22 (110.92, 134.56)
	NSP+ZOC/NSP or NSP+ZOC/ZOC†	41	0.88 (81.26, 96.08)	1.01 (88.76, 114.86)	1.02 (92.90, 112.29)
AUC_{last} (ng·hr/mL)	NS/NSP or NS/ZOC†	42	0.97 (88.89, 106.30)	1.23 (112.36, 133.57)	1.41 (128.67, 155.44)
	NS/NSP+ZOC	41	1.06 (96.95, 115.77)	1.12 (102.64, 122.02)	1.19 (108.57, 131.40)
	NSP+ZOC/NSP or NSP+ZOC/ZOC†	41	0.92 (83.90, 100.33)	1.09 (100.48, 119.27)	1.18 (107.83, 130.01)
%Fe(0-96h) Total‡	NS/NSP	41	0.99 (93.37, 105.09)	NA	NA
	NS/NSP+ZOC	40	1.01 (94.99, 106.75)	NA	NA
	NSP+ZOC/NSP	41	0.98 (92.53, 104.23)	NA	NA

NA: Not applicable.

NS: Niacin ER/ Simvastatin IR combination tablet.

NSP: ER Niacin tablet; ZOC: IR Simvastatin tablet.

* The 90% CI for the LSM ratios are expressed in percentages

† For NUA, ratios of NS/NSP and NSP+ZOC/NSP were determined. For simvastatin and simvastatin acid, ratios of NS/ZOC and NSP+ZOC/ZOC were determined

‡ Combined urinary recovery of niacin, NUA, MNA, and 2PY.

Source: Section 5.3.1.2

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/s/

Sang Chung
1/22/2008 02:18:03 PM
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Sally Choe
1/23/2008 07:10:03 AM
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