CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

CLINICAL PHARMACOLOGY AND BIOPHARMACEUTICS REVIEW(S)

Clinical Pharmacology and Biopharmaceutics Review

NDA:	21-249
Brand Name:	Nicostatin™ Tablets
Generic Name:	Niacin extended-release and lovastatin tablets
Strength(s):	500/20 mg (500 mg niacin and 20 mg lovastatin), 750/20 mg, and 1000/20 mg
Sponsor:	Kos Pharmaceutics, Inc. 14875 NW 77th Avenue, Suite 100 Miami Lakes, FL 33014
Submission Date:	21-September-2000
Submission Type:	Original Application – New Combination
Reviewer:	Sang M. Chung, Ph.D.
Team Leader:	Hae-Young Ahn, Ph.D.

SYNOPSIS

The sponsor has submitted original NDA 21-249 (Nicostatin™) for a fixed-combination of niacin and lovastatin tablet. Niacin is a B-complex vitamin and antihyperlipidemic agent, and lovastatin is a cholesterol-lowering agent isolated from a strain of *Aspergillus terreus*. Nicostatin comprises a niacin extended-release tablet — (Niaspan®) ——— immediate-release lovastatin. Tablet strengths of 500/20 (niacin 500 mg and lovastatin 20 mg), 750/20, and 1000/20 are proposed for commercial use. This submission is intended to support marketing approval for Nicostatin tablets —— manufactured by the sponsor in Edison, New Jersey, and ——— or the sponsor facilities in Edison, NJ.

Three pharmacokinetics studies have been conducted in humans to define the pharmacokinetics and bioavailability of niacin and lovastatin from Nicostatin: 1. A pilot study of the comparative bioavailability, 2. A four-way comparative bioavailability of Nicostatin versus Niaspan (reference of niacin) and Mevacor® (reference of lovastatin), and 3. A three-way crossover study of the effect of food on the bioavailability of Nicostatin tablets. All the studies were single-dose, open-label studies with oral administration. Administration of the study drug once-daily, with a low-fat snack, prior to bedtime (10 to 11 PM) was integrated to these studies and the proposed Nicostatin labeling recommends the same dosing. The bio-review of the Niaspan NDA indicated that administration with either high fat or low fat meal results in improved exposure to niacin and high fat meal would not result in dose dumping and increased adverse events.

A number of analytes were determined in these studies. For niacin bioavailability, plasma samples were analyzed for niacin and nicotinuric acid (NUA, a major metabolite), and urine samples were analyzed for niacin, NUA, and two additional major metabolites. For lovastatin bioavailability, plasma samples were analyzed for lovastatin, lovastatin acid, and/or total HMG-CoA (3-hydroxy-3-methylglutaryl-coenzyme A) reductase inhibition.

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Drug-drug interaction, formulation interaction, and food effect on the formulation are the major concern in the development of Nicostatin, a fixed-combination tablet.

Is there any drug-drug interaction between niacin and lovastatin ?
Pharmacokinetics and bioavailability of niacin and lovastatin were assessed for Niaspan and Mevacor (Niaspan+Mevacor) compared to Niaspan or Mevacor. There was neither lovastatin effect on niacin bioavailability nor niacin effect on lovastatin bioavailability. However, C_{max} of lovastatin acid when given Niaspan and Mevacor were 78% of that when given Mevacor alone with 70-87% of 90% CI.

Is there any formulation interaction ?
Formulation interaction was assessed by comparing pharmacokinetics of Nicostatin with those of Niaspan and lovastatin. Pharmacokinetic assessment showed no formulation interaction between Nicostatin and Niaspan+Mevacor. *In vitro* dissolution profiles were also compared. Dissolution profiles for niacin were quite similar for Niaspan and Nicostatin [redacted] Lovastatin dissolution from Nicostatin and Mevacor was quite different at 15 and 30 minutes, but similar at 45 and 60 minutes [redacted]

Is there any food effect on Nicostatin ?
Food effect on Nicostatin was evaluated by relative bioavailability studies. Significant food effect on niacin and lovastatin was documented. The study showed that administration with low and high fat meal resulted in increased systemic exposure for niacin and lovastatin.

RECOMMENDATION

The Office of Clinical Pharmacology and Biopharmaceutics / Division of Pharmaceutical Evaluation-II (OCPB/DPE-II) has reviewed NDA21-249 (Nicostatin™) submitted on 21-September-2000. The submission is acceptable to OCPB/DPE-II provided Nicostatin be approved as a convenience product. [redacted] The LABELING COMMENTS and RECOMMENDATION should be sent to the sponsor as appropriate.

Sang M. Chung, Ph.D. Date
Division of Pharmaceutical Evaluation II
Office of Clinical Pharmacology and Biopharmaceutics

Briefing:
- Date: 15-May-2001
- Attendee: Drs. Henry Malinowski, John Hunt, and Hae-Young Ahn

Final version signed by Team Leader

Hae-Young Ahn, Ph.D. Date

Cc: NDA 21-249 (orig., 1 copy), HFD-510 (Koch), HFD-850 (Lee), HFD-870 (Chung, Ahn, Malinowski), CDR
Code: AP

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LIST OF ABBREVIATIONS

Abbreviation	Definition
2PY	N-methyl-2-pyridone-5-carboxamide
4PY	N-methyl-4-pyridone-5-carboxamide
AGENCY	Food and Drug Administration
ANOVA	analysis of variance
AUC_{last}	area under the curve from time 0 to last measurable concentration (ss indicating at steady-state)
BE	Bioequivalence
C_{max}	maximum (plasma) concentration (ss indicating at steady-state)
CHD	coronary heart disease
CI	Confidence interval
CYP	cytochrome P-450
ER	extended-release
HDL-C	high-density lipoprotein cholesterol
HMG-CoA	3-hydroxy-3-methylglutaryl-coenzyme A
Kos	Kos Pharmaceuticals, Inc.
LDL-C	low-density lipoprotein cholesterol
MNA	N-methylnicotinamide
NAD	nicotinamide adenine dinucleotide
NCEP	National Cholesterol Education Program
NUA	nicotinuric acid
SGF	simulated gastric fluid
SIF	simulated intestinal fluid
SPONSOR	Kos Pharmaceuticals
TG	Triglyceride
T_{max}	time of maximum (plasma) concentration
Total HMG-CoA RI	Total HMG-CoA reductase inhibition
Total Recovery	recovery of niacin dose in urine, usually as niacin, NUA, MNA, and 2PY combined over 96 hours

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QUESTION BASED REVIEW

1. What are the bioavailability metrics for niacin and lovastatin ?

1-1 Niacin

Dr. Fossler in his Niaspan NDA review indicated that plasma niacin concentrations were too low and variable to characterize pharmacokinetics after administrations. Therefore, he proposed that plasma C_{max} of NUA, one of major niacin metabolite, be used to measure the rate of niacin absorption because its formation was dependent on input rate of niacin. Also, amount of niacin and metabolites excreted in urine was decided as a measure of the extent of absorption. Since Nicostatin tablets contain the same niacin tablet as Niaspan as — tablets, plasma C_{max} of NUA and total urinary excretion of niacin and metabolite were used to characterize the niacin absorption rate and extent, respectively.

1-2 Lovastatin

The sponsor proposed plasma lovastatin, lovastatin acid, and total HMG-CoA reductase inhibitory activity (HMG-CoA RI) as bioavailability metrics. Since HMG-CoA RI has not been correlated with either parent compounds or active metabolite, it would be used as a secondary metrics.

2. Why a fixed-combination (Nicostatin™) ?

Nicostatin™ tablets contain a niacin extended-release (ER) tablet and immediate-release lovastatin.

Nicostatin is expected to effectively shift major lipid parameters in a favorable direction by combining the potent LDL-C-lowering effect of lovastatin with the effect of niacin to favorably alter LDL-C, HDL-C, and other lipid parameters [e.g., apolipoprotein B, TG, Apo A-I, lipoprotein (a)].

3. Was there any drug-drug interaction between niacin and lovastatin ?

Bioavailability of niacin and lovastatin from the Nicostatin™ formulation were evaluated in a randomized, single-dose, open-label, 4-way crossover study. Each subject received two Nicostatin 1000/20 mg tablets, two Niaspan 1000 mg tablets, two Mevacor 20 mg tablets, and two Niaspan 1000 mg tablets with two Mevacor 20 mg tablets. Comparisons between treatments were made by 90% confidence intervals for the parameter ratios calculated with natural log-transformed data. Treatments of which the 90% confidence interval was within ——— % were considered equivalent.

It was concluded that there was no significant drug-drug interaction between niacin and lovastatin.

3-1 Lovastatin Effect on Niacin Bioavailability

The rate and extent of niacin absorption were essentially identical for Niaspan coadministered with Mevacor® relative to Niaspan®, as shown in the table and figure below. The rate and extent of niacin absorption from Nicostatin relative to Niaspan were also similar. These data indicated that the presence of lovastatin did not alter niacin absorption.

Table Niacin Bioavailability from Niaspan coadministered with Mevacor

Analyte and Parameter	Ratio (90% confidence interval) for: Niaspan + Mevacor compared to Niaspan alone
NUA C_{max}	97% (91 – 104)†
Urine Total Recovery	98% (93 – 103)†

† Meets bioequivalence criteria of 90% confidence interval within

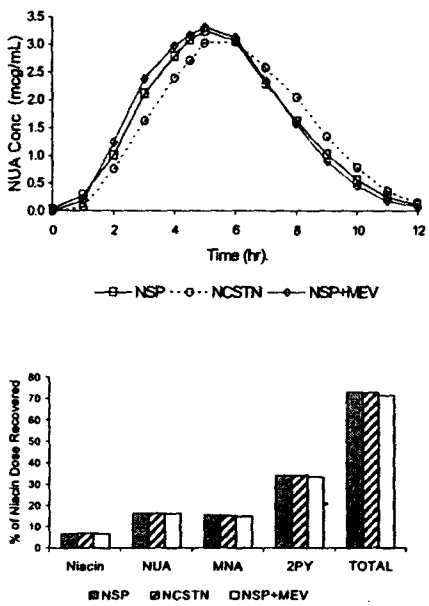

Figure Niacin Bioavailability from Niaspan coadministered with Mevacor.

3-2 Niacin Effect on Lovastatin Bioavailability

Based on analysis of parent drug data, there was no difference on lovastatin bioavailability between Mevacor coadministered with Niaspan and Mevacor alone (table and figure below).

Lovastatin acid data similarly indicated high lovastatin bioavailability from Niaspan+Mevacor relative to Mevacor alone but C_{max} of lovastatin acid, major active metabolite, was significantly lower from Mevacor+Niaspan than Mevacor alone (Table). In addition, the total HMG-CoA reductase inhibition assay, measured all potentially active species, provide a pharmacodynamic measure of therapeutic equivalence between Niaspan+Mevacor relative to Mevacor alone.

Considered together, the data from all three analytes indicate that the presence of niacin does not alter significantly lovastatin absorption.

Table Lovastatin Bioavailability from Mevacor coadministered with Niaspan

Analyte	Ratio (90% confidence interval) for: Niaspan + Mevacor compared to Mevacor alone	
	C_{max}	AUC_{last}
LOVASTATIN	102% (91-114)†	114% (106-123)†
Lovastatin acid	78% (70-87)	98% (90-106)†
Total HMG-CoA RI	94% (86-103)†	105% (100-111)†

† Meets (or essentially meets) bioequivalence criteria of 90% confidence interval within

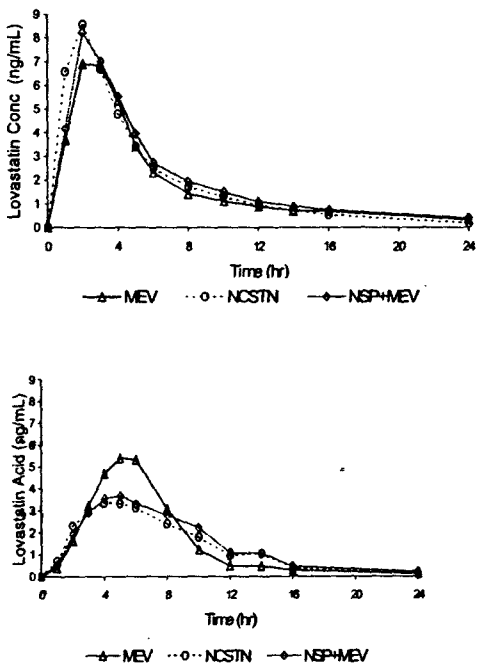

Figure Lovastatin Bioavailability from Mevacor coadministered with Niaspan

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4. Was there any formulation interaction ?

Formulation interaction was assessed by *in vivo* bioequivalence studies comparing Nicostatin with Niaspan+Mevacor. It was concluded that there was no significant formulation interaction.

4-1 *In vivo* formulation equivalence

In vivo BE of niacin and lovastatin from the Nicostatin™ formulation were evaluated in a single-dose, 4-way crossover study (also refer section 3). The results are summarized in Tables 4-1-1 and 4-1-2 and indicate that there is no formulation interaction.

Table 4-1-1 Niacin Bioavailability from Nicostatin

Analyte and Parameter	Ratio (90% confidence interval) for: Nicostatin compared to Niaspan + Mevacor
NUA C_{max}	104% (98 – 111)†
Urine Total Recovery	103% (98 – 108)†

† Meets bioequivalence criteria of 90% confidence interval within

Table 4-1-2 Lovastatin Bioavailability from Nicostatin

Analyte	Ratio (90% confidence interval) for: Nicostatin compared to Niaspan + Mevacor	
	C_{max}	AUC_{last}
LOVASTATIN	111% (99-124)†	95% (89-102)†
Lovastatin acid	96% (86-107)†	90% (83-98)†
Total HMG-CoA RI	110% (101-120)†	99% (94-105)†

† Meets (or essentially meets) bioequivalence criteria of 90% confidence interval within

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4-2 Dissolution profile

Dissolution profiles for the drugs used in this study are shown in Figures 4-2-1 and 4-2-2. Dissolution profiles for niacin were quite similar for the niacin — and Nicostatin —— Lovastatin dissolution profiles from Nicostatin and Mevacor were quite different —— However, the two products were bioequivalent (lovastatin component).

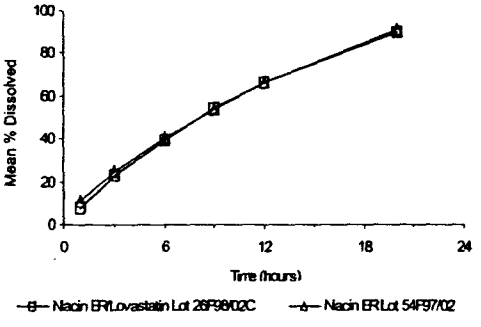

Figure 4-2-1. Mean Niacin Dissolution Profiles

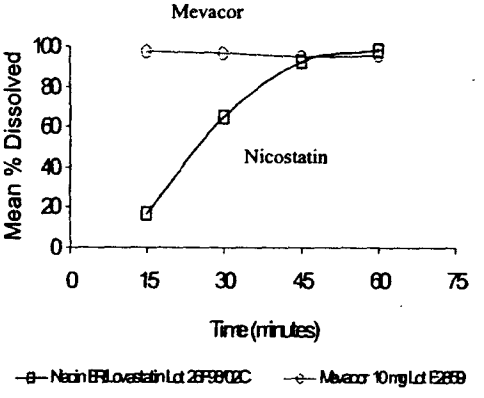

Figure 4-2-2. Mean Lovastatin Dissolution Profiles

5. Was the Proposed Dissolution method and specification of Nicostatin Acceptable ?

Dissolution method and specification for niacin is same as the approved method for Niaspan and those are acceptable. For lovastatin, the sponsor proposed dissolution method that is different from USP lovastatin tablets and it is acceptable for quality assurance.

5-1. Niacin Component

The release of niacin from niacin ER — tablets and from Nicostatin tablets was determined using USP Apparatus I (baskets) and 900 ml of deionized water at 37°C with continuous mixing (100 RPM) which is the approved dissolution method and specification for Niaspan.

Table Dissolution specification for niacin

Time (hour)	Specification (mean % label claim)
1	——
3	——
6	——
9	——
12	——
20	——

5-2. Lovastatin Component

The release of lovastatin from Nicostatin tablets was determined using USP Apparatus I (baskets) and 900 ml of dissolution medium (sodium phosphate and 0.5% sodium dodecyl sulfate) at 37°C with continuous mixing — RPM).

The proposed method is different from USP lovastatin tablets method of Apparatus II at 50 RPM. According to the sponsor, the method was selected because ——— of tablets to the paddles during USP Apparatus II method. The Agency concurred with their dissolution method in an industry meeting.

The sponsor has proposed the specification of Q= —— in 45 minutes, which appears to be reasonable to the Agency.

Table. Lovastatin Dissolution from Representative Nicostatin Lots

Time (min)	Mean % of LC Dissolved (Range), by Tablet Strength and Lot Number						
	500/10	500/20		750/20		1000/20	
	26F98/02*	56F99/02*	980204*	49F99/02*	980241*	50F99/02*	980244*
15	19 —	23 —	24 —	13 —	16 —	10 —	11 —
30	66 —	71 —	72 —	50 —	55 —	44 —	49 —
45	93 —	95 —	95 —	80 —	85 —	74 —	82 —
60	99 —	100 —	97 —	93 —	96 —	90 —	97 —

LC = Label claim or theoretical amount; NA = Not applicable
——— . tablets were tested for lot 50F99/02; otherwise, — tablets were tested for each lot

*: List of — manufacturing site, —— site, and study objective

Lot*	— Manufacturing Site	—— Site	PK study	Clinical study
26F98/02	Hollywood	Hollywood	Pilot relative BA	
980246	Hollywood	Hollywood		Dose response (active control)
56F99/02	Edison	Edison		
980204	Edison	——		Dose ranging (active control)
49F99/02	Edison	Edison		Long term safety and efficacy
980241	Edison	——		Dose ranging (active control)
50F99/02	Edison	Edison	4-way relative BA, Food effect	Phase 3b, Long term safety and efficacy
980244	Edison	——		Dose ranging (active control)

*: Lot size was more than —— tablets except 26F98/02 (—— tablets).

6. Was there any significant food effect on Nicostatin ?

The food effect on Nicostatin was assessed by *in vivo* BE study with a randomized, single-center, single-dose, open-label, 3-way crossover study; fasting, high fat and low fat. There was a significant food effect on Nicostatin.

6-1 Niacin

Niacin bioavailability was greater when administered after either snack compared to fasting administration (see table and figure in the next page). For example, high fat food increases niacin extent and rate of absorption about 30% and 38%, respectively, compared to fasting. There was no difference on BA of niacin between low fat snack and high fat meal.

Table Effect of Food on Niacin Bioavailability (Protocol CP-98-010419)

Comparison and Parameter	Ratio (90% Confidence Interval by Analyte)
HIGH/FAST	
NUA C_{max}	138 (122 – 157)
Total Urinary Recovery	130 (119 – 143)
LOW/FAST	
C_{max}	155 (137 – 175)
Total Urinary Recovery	122 (111 – 133)
HIGH/LOW	
C_{max}	89 (79 – 101)
Total Urinary Recovery	107 (98 – 117)†

Confidence interval calculation based on natural log-transformed data.
†Meets (or essentially meets) equivalence criteria of within —— %.

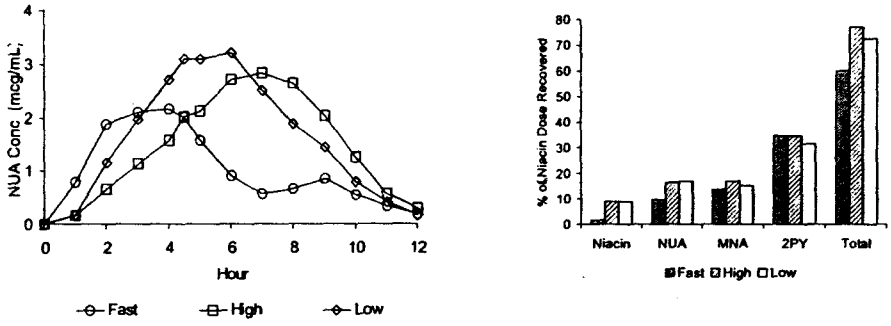

Figure Effect of Food on Niacin Bioavailability

6-2 Lovastatin

Lovastatin bioavailability was greater when administered after either snack compared to fasting administration based on AUC from 0 to 4 hours (AUC_{0-4}), which was used for lovastatin instead of AUC_{0-last} (see table and figure below in the next page). Lovastatin AUC_{0-last} was used in comparisons of high and low fat meal. Bioavailability of lovastatin acid was significantly reduced by low fat snack compared to fasting (76 % and 61 % for C_{max} and AUC_{0-last}, respectively, compared to fasting). No conclusion was made in this regarding by the sponsor.

The interpretation of food effect based on AUC_{0-4} is not acceptable because there is lack of scientific background for introduction of the parameter.

Contrary to the conclusion by the sponsor, extent of lovastatin bioavailability was decreased by either high or low fat snack based on AUC_{0-last}.

Table . Effect of Food on Lovastatin Bioavailability (Protocol CP-98-010419)

Comparison and Parameter	Ratio (90% Confidence Interval by Analyte)	
	Lovastatin	Lovastatin acid
HIGH/FAST		
Cmax	148 (130 – 170)	121 (102 – 144)
AUC_{0-4}	140 (122 – 160)	-
AUC_{0-last}	74 (66-83)	85 (74-98)
LOW/FAST		
Cmax	121 (106 – 138)	76 (64-90)
AUC_{0-4}	123 (107 – 140)	-
AUC_{0-last}	76 (68-85)	61 (53-71)
HIGH/LOW		
Cmax	123 (107 – 140)	160 (135 – 191)
AUC_{0-last}	97 (87 – 109) †	139 (120 – 161)

Confidence interval calculation based on natural log-transformed data.
†Meets (or essentially meets) equivalence criteria of within ——— % for AUC.

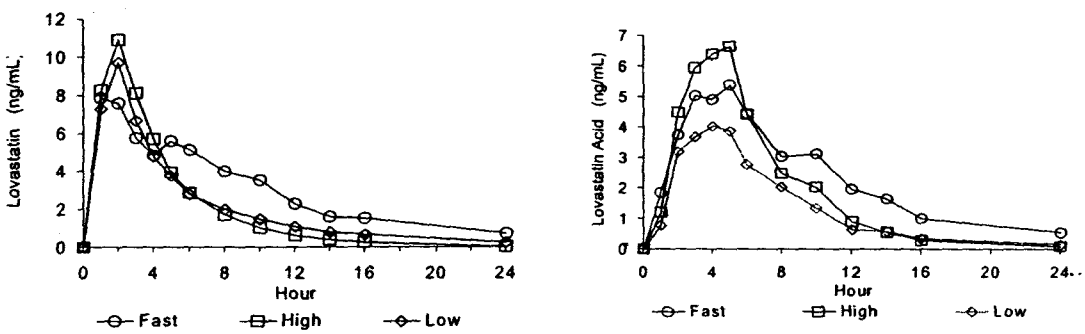

Figure Effect of Food on Lovastatin Bioavailability

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REVIEWERS COMMENTS

Major regulatory concerns were assessed in the development of Nicostatin. There was no significant drug-drug interaction between Niaspan and Mevacor because Niaspan+Mevacor essentially met bioequivalence criteria compared to Niaspan or Mevacor alone. Also, it was concluded that there was no significant formulation interaction because Nicostatin showed bioequivalence compared to Niaspan+Mevacor. However dissolution profile was different between Nicostatin and Mevacor (———). Therefore, different dissolution method and specification was proposed.

During review status meetings the followings were learned:

1. Pivotal clinical trials were active control trials; Nicostatin efficacy was compared with lovastatin's.
2. ———————————————————————————
3. Efficacy of lovastatin was found to be much less than historical data of Mevacor.

Therefore, it was decided that the sponsor need to conduct a bioequivalence study comparing placebo lovastatin 1000/20 mg strength and Mevacor 20 mg in order to interpret the efficacy data as an initial therapy. However, the bioequivalence study may not be needed if the sponsor intends to claim the product as a convenience product. This decision was communicated with the sponsor on 05-March-2001.

LABELING COMMENTS

Pharmacokinetics

Absorption and Bioavailability

NICOSTATIN

In single-dose studies of NICOSTATIN, rate and extent of niacin and lovastatin absorption were bioequivalent to that from Niaspan® and Mevacor® tablets, respectively. After administration of two NICOSTATIN 1000/20 tablets, peak niacin concentrations averaged about 18 mcg/mL and occurred about 5 hours after dosing; about 72% of the niacin dose was absorbed. Peak lovastatin concentrations averaged about 11 ng/mL and occurred about 2 hours after dosing.

[ ]

Comment:

- It is recommended that the degree of food effect be presented based on niacin bioavailability metrics, which are plasma NUA and total extent in urine. Also, C_{max} and AUC should not be pooled for average because the two parameters represent independent measures.
- It is recommended that the effect of food on extent of lovastatin bioavailability be presented based on total AUC ($AUC_{0\text{-}last}$) instead of partial AUC ($AUC_{0\text{-}4}$).

Niacin

Due to extensive ; and saturable ; first-pass metabolism, niacin concentrations in the general circulation are dose dependent and highly variable. Peak steady-state niacin concentrations were 0.6, 4.9, and 15.5 mcg/mL after doses of 1000, 1500, and 2000 mg Niaspan® once daily (given as two 500 mg, two 750 mg, and two 1000 mg tablets, respectively).

Lovastatin
Lovastatin appears to be incompletely absorbed after oral administration. Because of extensive hepatic extraction, the amount of lovastatin reaching the systemic circulation as active inhibitors after oral administration is low (<5%) and shows considerable inter-individual variation. Peak concentrations of active and total inhibitors occur within 2 to 4 hours after Mevacor® administration.

Lovastatin absorption appears to be increased by at least 30% by grapefruit juice; however, the effect is dependent on the amount of grapefruit juice consumed and the interval between grapefruit juice and lovastatin ingestion.

With a once-a-day dosing regimen, plasma concentrations of total inhibitors over a dosing interval achieved a steady-state between the second and third days of therapy and were about 1.5 times those following a single dose of Mevacor®.

Distribution

Niacin
Niacin is less than 20% bound to human serum proteins and distributes into milk. Studies using radiolabeled niacin in mice show that niacin and its metabolites concentrate in the liver, kidney, and adipose tissue.

Lovastatin
Both lovastatin and its beta-hydroxyacid metabolite are highly bound (>95%) to human plasma proteins. Distribution of lovastatin or its metabolites into human milk is unknown; however, lovastatin distributes into milk in rats. In animal studies, lovastatin concentrated in the liver, and crossed the blood-brain and placental barriers.

Metabolism

Niacin
Niacin undergoes rapid and extensive first-pass metabolism that is dose-rate specific and, at the doses used to treat dyslipidemia, saturable. In humans, one pathway is through a simple conjugation step with glycine to form nicotinuric acid (NUA). NUA is then excreted, although there may be a small amount of reversible metabolism back to niacin. The other pathway results in the formation of NAD. It is unclear whether nicotinamide is formed as a precursor to, or following the synthesis of, NAD. Nicotinamide is further metabolized to at least N-methylnicotinamide (MNA) and nicotinamide-N-oxide (NNO). MNA is further metabolized to two other compounds, N-methyl-2-pyridone-5-carboxamide (2PY) and N-methyl-4-pyridone-5-carboxamide (4PY). The formation of 2PY appears to predominate over 4PY in humans.

Lovastatin
Lovastatin undergoes extensive first-pass extraction and metabolism by cytochrome P450 3A4 in the liver, its primary site of action. The major active metabolites present in human plasma are the beta-hydroxyacid of lovastatin (lovastatin acid), its 6'-hydroxy derivative, and two additional metabolites.

Elimination
NICOSTATIN
Niacin is primarily excreted in urine mainly as metabolites. After a single dose of NICOSTATIN, at least 60% of the niacin dose was recovered in urine as unchanged niacin and its metabolites. The plasma half-life for lovastatin was about 4.5 hours in single-dose studies.

Comment:
- It is recommended that the statement require further clarification. Otherwise it could be interpreted as major component is niacin in urine.

Niacin

The plasma half-life for niacin is about 20 to 48 minutes after oral administration and dependent on dose administered. Following multiple oral doses of NIASPAN®, up to 12% of the dose was recovered in urine as unchanged niacin depending on dose administered. The ratio of metabolites recovered in the urine was also dependent on the dose administered.

Lovastatin

Lovastatin is excreted in urine and bile, based on studies of Mevacor®. Following an oral dose of radiolabeled lovastatin in man, 10% of the dose was excreted in urine and 83% in feces. The latter represents absorbed drug equivalents excreted in bile, as well as any unabsorbed drug.

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Labeling

Appendix 2. Study Reports

TITLE: A Pilot Study of the Comparative Bioavailability of a Niaspan® and Lovastatin Combination Tablet versus Coadministration of Niaspan® and Mevacor® (Protocol 97/07)

ABSTRACT

This open-label, randomized, single-dose, two-way crossover study was designed to compare the single-dose bioavailability of Nicostatin™, a combination tablet of extended-release niacin ——— immediate-release lovastatin, relative to coadministration of equivalent doses of Niaspan® (extended-release niacin) and Mevacor® (immediate-release lovastatin).

Twenty-four healthy, nonsmoking male and female subjects, 40 to 70 years-of-age, inclusive, were to participate in the study. Each subject received, in random sequence, each of the following treatments administered immediately following a low-fat snack:

Reference:	1500 mg extended-release niacin (3 x 500 mg tablets; lot 54F97/02A) and 30 mg Mevacor (3 x 10 mg lovastatin tablets; lot E2859)
Test:	1500/30 mg Nicostatin™ (3 tablets, each containing 500 mg niacin extended-release and 10 mg lovastatin; lot 26F98/02C)

Extended-release niacin ——— the same lot were used both in the Nicostatin tablets and in place of Niaspan® tablets in the Reference treatment; manufacture of these ——— essentially equivalent to Niaspan® manufacture. Alcohol- and caffeine-free meals were administered throughout the study and were consistent across all periods. Meals were controlled for niacin and fat content throughout the study periods. Each dose was administered with at least 240 mL of water at approximately 2200 following a low-fat snack. Subjects were confined for approximately three days for each treatment, and treatments were separated by a washout period of at least ten days. Blood samples were obtained prior to dosing and for 18 hours after dosing. Urine was collected for 24 through 12 hours prior to dosing and for 12 hours after dosing. Plasma was analyzed for niacin and NUA or lovastatin acid concentrations (or all three; selected samples for each), and urine was analyzed for niacin and NUA concentrations.

Twenty-four healthy, nonsmoking subjects (12 males and 12 females) were enrolled in the study, received two doses of study medication, provided safety information and completed the study.

No clinically significant changes in physical examinations, blood pressure, pulse rate, oral temperature, respiration rate, laboratory test results or electrocardiograms were seen.

Fifteen subjects who received study drug reported at least one adverse event during the study. Overall, the most frequently occurring treatment-emergent adverse events were vasodilation (in 29.2%-33.3% of subjects) and pruritus (in 20.8%-29.2% of subjects). Adverse events were mild (97%) or severe (3%) in intensity; none were moderate. No serious adverse events occurred during the study.

Bioavailability data are summarized in the table below. Conclusions of bioequivalence were based on classical 90% confidence intervals (CIs) for the ratio of means from natural log-transformed data being within the conventional ——— % limits for lovastatin acid Cmax, $AUC_{0\text{-last}}$ and $AUC_{0\text{-inf}}$ and for NUA Cmax only. All data were rounded to three significant figures except for Tmax, which was rounded to two significant figures. Concentrations were presented with no more than three decimal places.

Table 1 Summary of Bioavailability Parameters and Statistics

		Mean	SD	%CV	Statistics[§] Ratio (%)	90% CI
NIACIN						
NUA Cmax (μg/mL)						
	Reference	1.64	0.90	55	107	95 - 120[‡]
	Test	1.70	0.72	43		
Niacin+NUA Recovery (% of dose)						
	Reference	6.81	4.11	60	116	101 - 134
	Test	7.78	4.23	54		
LOVASTATIN ACID						
Cmax (ng/mL)						
	Reference	4.34	3.48	80	102	89 - 117[‡]
	Test	4.70	5.68	121		
$AUC_{0\text{-last}}$ (ng•hr/mL)						
	Reference	28.0	20.0	71	90	80 - 101[‡]
	Test	27.2	27.8	102		
$AUC_{0\text{-inf}}$ (ng•hr/mL)						
	Reference	29.8	20.8	70	89	80 - 100[‡]
	Test	29.0	29.7	102		
Tmax (hr)						
	Reference	4.8	NA	NA	0.341[†]	NA
	Test	4.5	NA	NA		

Data are from 24 subjects. [§]Ratio and confidence interval (CI) calculations are based on analysis of natural log-tranformed data. Ratio is calculated as Test/Reference. [‡]A 90% CI within ——— % suggests bioequivalence of the two treatments. [†]p-value by Wilcoxon Signed-Rank test of untransformed Tmax data. NA = Not applicable.

Conclusions:

- Niacin and lovastatin were both well absorbed from the Nicostatin 500/10 formulation.
- Based on NUA Cmax, Nicostatin and the extended-release niacin ⌐ tablets were equivalent in the rate of niacin absorption. Urine recovery data for niacin and NUA combined also suggested equivalence in niacin absorption rate.
- Based on plasma lovastatin acid data, Nicostatin and Mevacor tablets were equivalent in the rate and extent of lovastatin absorption.
- The Nicostatin 500/10 formulation was well tolerated by the subjects participating in this study.

APPEARS THIS WAY
ON ORIGINAL

Title: The Comparative Bioavailability of a Niacin and Lovastatin Combination versus Niaspan® and Mevacor® (Protocol CP-98-010418)

SYNOPSIS

Sponsor/Company: Kos Pharmaceuticals, Inc. (Kos) Finished Product: Nicostatin™ Active Ingredients: niacin and lovastatin	Individual Study Table	*(For National Authority Use Only)*

Title of Study:	The Comparative Bioavailability of a Niacin and Lovastatin Combination versus Niaspan® and Mevacor®
Principal Investigator:	[ ]
Study Center:	[ ]
Publication (Reference):	None
Study period : date of first clinic admission: date of last clinic discharge:	7 weeks 25 September 1999 10 November 1999
Phase of development:	Phase I

Objective: The purpose of this study is to compare the bioavailability of niacin and lovastatin from a combination tablet relative to administration of Niaspan alone, Mevacor alone, and coadministration of Niaspan and Mevacor.

Methodology:

This was a randomized, single-dose, open-label, 4-way crossover study. Drop-outs were not replaced. Each subject received each of four treatments on separate occasions at least 10 days apart: two Nicostatin 1000/20 mg tablets, two Niaspan 1000 mg tablets, two Mevacor 20 mg tablets, and two Niaspan 1000 mg tablets with two Mevacor 20 mg tablets. Each dose was administered with 240 mL of water beginning at approximately 2200 after a low-fat snack. Meals (breakfast, lunch, dinner, and evening snack) controlled for niacin and fat content were provided during each treatment period.

Blood samples were obtained within 30 minutes prior to dosing and at frequent intervals for 24 hours after dosing; urine was collected for 24 hours prior to and 96 hours after dosing. Plasma was analyzed for niacin, NUA, lovastatin, lovastatin acid, and total HMG CoA reductase inhibition. Urine was analyzed for niacin and its three major metabolites (NUA< MNA, 2PY). Subjects were housed during the 6-day study period of each treatment.

Number of Subjects (Planned and Analyzed): 40 subjects planned; data analyzed from 40 subjects

Diagnosis and main criteria for inclusion: Healthy, nonsmoking male and female subjects, 40 to 70 years-of-age, with no clinically-significant abnormalities based on physical exam, laboratory tests, ECG, or medical history

Test product, dose and mode of administration, batch number:
Nicostatin 1000/20 (niacin extended-release [ER]/lovastatin) tablets; two tablets administered orally (dose = 2000 mg niacin with 40 mg lovastatin); bulk lot number 50F99/02, packaged lot number 50F99/02B; abbreviated as NCSTN

Sponsor/Company: Kos Pharmaceuticals, Inc. (Kos)	Individual Study Table	*(For National Authority Use Only)*
Finished Product: Nicostatin™		
Active Ingredients: niacin and lovastatin		

Reference therapies, dose and mode of administration, batch number:
Niaspan (niacin ER, Kos) 1000 mg tablets; two tablets administered orally (2000 mg dose); bulk lot number 9905600001, packaged lot number 9908100002; abbreviated as NSP
Mevacor (lovastatin, Merck) 20 mg tablets; two tablets administered orally (40 mg dose); commercial lot number J0842; abbreviated as MEV
Niaspan 1000 mg tablets with Mevacor 20 mg tablets; two tablets of each administered orally (dose = 2000 mg niacin with 40 mg lovastatin); lot numbers same as indicated above; abbreviated as NSP+MEV

Duration of treatment: Single-dose administration on four separate occasions, each administration separated by at least 10 days

Criteria for evaluation:
Pharmacokinetics:
Pharmacokinetic data were analyzed from all subjects who completed at least one treatment period. Niacin bioequivalence was assessed by NUA maximum plasma concentrations (Cmax) and total urine recovery (niacin and metabolites NUA, MNA, and 2PY) resulting from single-dose administration of 2000 mg niacin. Lovastatin bioequivalence was assessed by plasma lovastatin, lovastatin acid, and total HMG CoA reductase inhibition data resulting from single-dose administration of 40 mg lovastatin.

Safety:
Safety data were summarized and/or analyzed from all subjects who received at least one dose of study medication.

Statistical methods: For pharmacokinetic parameters, classical 90% confidence intervals were calculated for the ratio of least square means from natural log-transformed data. Confidence intervals within the conventional ——→ limits were used to conclude bioequivalence. No statistical tests were performed on the safety data.

SUMMARY OF RESULTS

Pharmacokinetics:
Mean NUA Cmax was 3.92, 3.97, and 3.83 mcg/mL for NSP, NCSTN, and NSP+MEV, respectively. Total recovery in the urine (niacin, NUA, MNA, and 2PY) for 96 hours after dosing was 73.0, 72.8, and 71.5% of the administered niacin dose for NSP, NCSTN, and NSP+MEV treatments, respectively. All three niacin-containing treatments were equivalent in both NUA Cmax and Total Recovery.

Mean lovastatin Cmax was 9.77, 11.2, and 9.72 ng/mL and mean lovastatin AUClast was 42.6, 46.3, and 49.1 ng*hr/mL for MEV, NCSTN, and NSP+MEV, respectively. All three lovastatin-containing treatments were equivalent in lovastatin Cmax and AUClast.

Mean lovastatin acid Cmax was 6.09, 4.48, and 4.63 ng/mL and mean lovastatin acid AUClast was 35.6, 31.7, and 35.0 ng*hr/mL for MEV, NCSTN, and NSP+MEV, respectively. Lovastatin acid Cmax was higher for MEV than for NCSTN or NSP+MEV (which were equivalent); lovastatin acid AUClast was equivalent for all three lovastatin-containing treatments.

Mean total HMG CoA reductase inhibition Cmax was 94.4, 98.0, and 87.8 nM-eq and mean AUClast was 472, 497, and 502 nM-eq*hr for MEV, NCSTN, and NSP+MEV, respectively. All three lovastatin-containing treatments were equivalent in both Cmax and AUClast for total HMG CoA reductase inhibition.

APPEARS THIS WAY
ON ORIGINAL

Sponsor/Company: Kos Pharmaceuticals, Inc. (Kos)	Individual Study Table	*(For National Authority Use Only)*
Finished Product: Nicostatin™		
Active Ingredients: niacin and lovastatin		

Safety:

No serious and unexpected adverse events occurred. The treatment-emergent adverse event reported most frequently for all four treatment groups was flushing.

CONCLUSIONS:

- The pharmacokinetics of niacin and lovastatin from Nicostatin relative to Niaspan and Mevacor were adequately characterized
- No clinically relevant interaction occurs between niacin and lovastatin when co-administered as either a single formulation or as separate formulations
- Niacin absorption from Nicostatin is bioequivalent with that from Niaspan alone and from Niaspan co-administered with Mevacor
- Lovastatin absorption from Nicostatin is bioequivalent with that from Mevacor alone and from Mevacor co-administered with Niaspan
- Niacin and lovastatin absorption from Niaspan co-administered with Mevacor is bioequivalent with that from Niaspan alone and Mevacor alone
- Study treatments were reasonably well tolerated since the most frequently reported adverse event after any treatment was flushing

APPEARS THIS WAY
ON ORIGINAL

Table 2 Plasma Niacin and NUA Bioavailability in the comparative bioavailability of a niacin and lovastatin combination (Nicostatin®) versus Niaspan® and Mevacor®

	Niacin			NUA				
	Mean	SD	%CV	Mean	SD	%CV	Ratio(%) [a]	90% CI
C_{max} (mcg/mL)								
NSP	18.2	14.1	77	3.92	1.57	40	NCS/NSP: 101	95 - 108 [†]
NCSTN (NCS)	17.8	12.4	70	3.97	1.61	41	N+M/NSP: 97	91 - 104 [†]
NSP+MEV (N+M)	18.0	15.3	85	3.83	1.64	43	NCS/N+M: 104	98 - 111 [†]
AUC_{last} (mcg*hr/mL)								
NSP	53.3	50.9	95	18.4	9.10	50	NA	NA
NCSTN (NCS)	52.4	46.2	88	18.0	8.81	49	NA	NA
NSP+MEV (N+M)	58.2	61.3	105	18.6	9.27	50	NA	NA
T_{max} (hr)								
NSP	5.2	1.5	29	5.4	1.5	28	NCS vs NSP: 0.244 [b]	
NCSTN (NCS)	5.4	1.6	30	5.7	1.6	29	N+M vs NSP: 0.762 [b]	
NSP+MEV (N+M)	5.2	1.4	28	5.3	1.4	26	NCS vs N+M: 0.107 [b]	

Niacin dose = 2000 mg in each treatment. N = 40. NA = Not Applicable.
[†] Suggests equivalence (i.e., 90% CI within ——— %).
[a] Ratio of the least square means of natural-log transformed NUA Cmax for treatments indicated.
[b] *p*-value by Wilcoxon Signed-Rank Test.
Data Source: Appendices B and G.

APPEARS THIS WAY
ON ORIGINAL

Table 3 Niacin urinary recovery in the comparative bioavailability of a niacin and lovastatin combination (Nicostatin®) versus Niaspan® and Mevacor®

	Mean	SD	%CV	Ratio(%)[a]	90% CI
Niacin Recovery (% of dose)					
NSP	6.73	5.44	81	NC	NC
NCSTN	7.01	5.21	74		
NSP+MEV	6.76	5.61	83		
NUA Recovery (% of dose)					
NSP	16.4	6.54	40	NC	NC
NCSTN	16.4	7.96	49		
NSP+MEV	16.3	7.89	48		
MNA Recovery (% of dose)					
NSP	15.6	5.39	35	NC	NC
NCSTN	15.3	5.92	39		
NSP+MEV	14.9	6.09	41		
2PY Recovery (% of dose)					
NSP	34.2	8.71	25	NC	NC
NCSTN	34.1	8.87	26		
NSP+MEV	33.5	10.2	31		
Total Recovery[b] (% of dose)					
NSP	73.0	11.5	16	NCS/NSP: 100	95 - 105 †
NCSTN (NCS)	72.8	9.95	14	NSP+M/NSP: 98	93 - 103 †
NSP+MEV (N+M)	71.5	12.6	18	NCS/N+M: 103	98 - 108 †

Niacin dose = 2000 mg in each treatment. N = 40 NC = Not Calculated.
† Suggests equivalence (i.e., 90% CI within ——— %).
[a] Ratio of the least square means of natural-log transformed Total Recovery for treatments indicated.
[b] Recovery of niacin, NUA, MNA, and 2PY combined.
Data Source: Appendices F and G.

APPEARS THIS WAY
ON ORIGINAL

Table 4 Plasma Lovastatin Bioavailability in the comparative bioavailability of a niacin and lovastatin combination (Nicostatin®) versus Niaspan® and Mevacor®

	Mean	SD	%CV	Ratio(%) [a]	90% CI
Cmax (ng/mL)					
MEV	9.77	7.31	75	NCS/MEV: 113	101 - 126 [†]
NCSTN (NCS)	11.2	8.40	75	N+M/MEV: 102	91 - 114 [†]
NSP+MEV (N+M)	9.72	6.05	62	NCS/N+M: 111	99 - 124 [†]
AUClast (ng*hr/mL)					
MEV	42.6	25.8	61	NCS/MEV: 109	101 - 117 [†]
NCSTN (NCS)	46.3	27.1	59	N+M/MEV: 114	106 - 123 [†]
NSP+MEV (N+M)	49.1	32.3	66	NCS/N+M: 95	89 - 102 [†]
Tmax (hr)					
MEV	2.6	1.0	40	NCS vs MEV: 0.042* [b]	
NCSTN (NCS)	2.2	1.1	49	N+M vs MEV: 0.083 [b]	
NSP+MEV (N+M)	2.3	0.8	36	NCS vs N+M: 0.564 [b]	
AUCinf (ng*hr/mL)					
MEV	48.1	30.3	63	NC	NC
NCSTN (NCS)	48.3	28.4	59	NC	NC
NSP+MEV (N+M)	56.5	39.8	71	NC	NC
k (1/hr)					
MEV	0.115	0.0680	59	NC	NC
NCSTN (NCS)	0.154	0.0623	40	NC	NC
NSP+MEV (N+M)	0.101	0.0562	56	NC	NC
t1/2 (hr)					
MEV	6.0 [c]	NC	NC	NC	NC
NCSTN (NCS)	4.5 [c]	NC	NC	NC	NC
NSP+MEV (N+M)	6.9 [c]	NC	NC	NC	NC

Lovastatin dose = 40 mg in each treatment. N = 40. NC = Not Calculated.

* Statistically significant at $p \leq 0.05$ level.

† Suggests equivalence (i.e., 90% CI within or slightly outside)

[a] Ratio of the least square means of the natural-log transformed parameter for treatments indicated.

[b] p-value by Wilcoxon Signed-Rank Test.

[c] Harmonic mean.

Data Source: Appendices C and G.

APPEARS THIS WAY
ON ORIGINAL

Table 5 Plasma Lovastatin Acid Bioavailability in the comparative bioavailability of a niacin and lovastatin combination (Nicostatin®) versus Niaspan® and Mevacor®

	Mean	SD	%CV	Ratio(%) [a]	90% CI
Cmax (ng/mL)					
MEV	6.09	3.31	54	NCS/MEV: 75	67 - 84
NCSTN (NCS)	4.48	2.42	54	N+M/MEV: 78	70 - 87
NSP+MEV (N+M)	4.63	2.34	51	NCS/N+M: 96	86 - 107 [†]
AUClast (ng*hr/mL)					
MEV	35.6	17.2	49	NCS/MEV: 89	82 - 96 [†]
NCSTN (NCS)	31.7	16.3	51	N+M/MEV: 98	90 - 106 [†]
NSP+MEV (N+M)	35.0	18.1	52	NCS/N+M: 90	83 - 98 [†]
Tmax (hr)					
MEV	4.9	1.3	27	NCS vs MEV: 0.467 [b]	
NCSTN (NCS)	4.8	2.6	55	N+M vs MEV: 0.068 [b]	
NSP+MEV (N+M)	6.0	2.5	42	NCS vs N+M: 0.028* [b]	
AUCinf (ng*hr/mL)					
MEV	37.6	17.3	46	NC	NC
NCSTN (NCS)	33.2	16.7	50	NC	NC
NSP+MEV (N+M)	36.9	18.5	50	NC	NC
k (1/hr)					
MEV	0.199	0.117	59	NC	NC
NCSTN (NCS)	0.202	0.0845	42	NC	NC
NSP+MEV (N+M)	0.170	0.0727	43	NC	NC
t1/2 (hr)					
MEV	3.5 [c]	NC	NC	NC	NC
NCSTN (NCS)	3.4 [c]	NC	NC	NC	NC
NSP+MEV (N+M)	4.1 [c]	NC	NC	NC	NC

Lovastatin dose = 40 mg in each treatment. N = 40. NC = Not Calculated.

* Statistically significant at $p \leq 0.05$ level.

[†] Suggests equivalence (i.e., 90% CI within ——— %).

[a] Ratio of the least square means of the natural-log transformed parameter for treatments indicated.

[b] p-value by Wilcoxon Signed-Rank Test.

[c] Harmonic mean.

Data Source: Appendices C and G.

APPEARS THIS WAY
ON ORIGINAL

Table 6 Plasma Total HMG CoA Reductase Inhibition Bioavailability in the comparative bioavailability of a niacin and lovastatin combination (Nicostatin®) versus Niaspan® and Mevacor®

	Mean	SD	%CV	Ratio(%) [a]	90% CI
Cmax (nM-eq)					
MEV	94.4	43.2	46	NCS/MEV: 103	95 - 113 [†]
NCSTN (NCS)	98.0	44.3	45	N+M/MEV: 94	86 - 103 [†]
NSP+MEV (N+M)	87.8	32.0	36	NCS/N+M: 110	101 - 120 [†]
AUClast (nM-eq*hr)					
MEV	472	173	37	NCS/MEV: 105	99 - 111 [†]
NCSTN (NCS)	497	188	38	N+M/MEV: 105	100 - 111 [†]
NSP+MEV (N+M)	502	215	43	NCS/N+M: 99	94 - 105 [†]
Tmax (hr)					
MEV	3.1	1.1	37	NCS vs MEV: 0.019* [b]	
NCSTN (NCS)	2.5	1.2	50	N+M vs MEV: 0.099 [b]	
NSP+MEV (N+M)	2.7	1.2	46	NCS vs N+M: 0.382 [b]	
AUCinf (nM-eq*hr)					
MEV	492	178	36	NC	NC
NCSTN (NCS)	515	190	37	NC	NC
NSP+MEV (N+M)	526	221	42	NC	NC
k (1/hr)					
MEV	0.208	0.0856	41	NC	NC
NCSTN (NCS)	0.195	0.0775	40	NC	NC
NSP+MEV (N+M)	0.159	0.0517	32	NC	NC
t1/2 (hr)					
MEV	3.3 [c]	NC	NC	NC	NC
NCSTN (NCS)	3.6 [c]	NC	NC	NC	NC
NSP+MEV (N+M)	4.3 [c]	NC	NC	NC	NC

Lovastatin dose = 40 mg in each treatment. N = 40. NC = Not Calculated.

* Statistically significant at $p \leq 0.05$ level.

[†] Suggests equivalence (i.e., 90% CI within ——— %).

[a] Ratio of the least square means of the natural-log transformed parameter for treatments indicated.

[b] p-value by Wilcoxon Signed-Rank Test.

[c] Harmonic mean.

Data Source: Appendices C and G.

APPEARS THIS WAY
ON ORIGINAL

Title: A Three-Way Crossover Study of the Effect of Food on the Bioavailability of Nicostatin™ Tablets (CP-98-010419)

SYNOPSIS

Sponsor/Company: Kos Pharmaceuticals, Inc. (Kos)	Individual Study Table	*(For National Authority Use Only)*
Finished Product: Nicostatin™		
Active Ingredients: niacin and lovastatin		

Title of Study:	A Three-Way Crossover Study of the Effect of Food on the Bioavailability of Nicostatin™ Tablets
Principal Investigator:	[ ]
Study Center:	[ ]
Publication (Reference):	None
Study period : date of first clinic admission: date of last clinic discharge:	4 weeks 1 March 2000 27 March 2000
Phase of development:	Phase I

Objective: The purpose of this study is to determine the effect of a high-fat and a low-fat snack on the bioavailability of Nicostatin tablets relative to administration under fasting conditions.

Methodology:

This was a randomized, single-center, single-dose, open-label, 3-way crossover study. Drop-outs were not replaced. Each subject received each of three treatments on separate occasions at least 10 days apart: two Nicostatin 1000/20 tablets (1000 mg niacin, 20 mg lovastatin/tablet), administered after a 10-hour fast; two Nicostatin 1000/20 tablets, administered after a low-fat snack; two Nicostatin 1000/20 tablets, administered after a high-fat snack. Each dose was administered with 240 mL of water beginning at approximately 2200. Meals (breakfast, lunch, dinner, and evening snack) controlled for niacin and fat content were provided during each treatment period.

Blood samples were obtained within 30 minutes prior to dosing and at frequent intervals for 24 hours after dosing; urine was collected for 24 hours prior to and 96 hours after dosing. Plasma was analyzed for niacin, NUA, lovastatin, lovastatin acid, and total HMG-CoA reductase inhibition. Urine was analyzed for niacin and its three major metabolites (NUA, MNA, 2PY). Subjects were confined during the 6-day study period of each treatment.

Number of Subjects (Planned and Analyzed): 27 subjects planned; data analyzed from 27 subjects

Diagnosis and main criteria for inclusion: Healthy, nonsmoking male and female subjects, 40 to 70 years-of-age, with no clinically-significant abnormalities based on physical exam, laboratory tests, ECG, or medical history

Test Treatment product(s), dose and mode of administration, batch number:
Nicostatin 1000/20 (niacin extended-release [ER]/lovastatin) tablets; bulk lot number 50F99/02, packaged lot number 50F99/02B.
Dose = 2 Nicostatin tablets (2000 mg niacin, 40 mg lovastatin) administered orally after a low-fat snack in Treatment = LOW and after a high-fat snack in Treatment = HIGH.

Reference therapy, dose and mode of administration, batch number:
Nicostatin 1000/20 (niacin ER/lovastatin) tablets; bulk and packaged lot numbers the same as above in the Test therapies.
Dose = 2 Nicostatin tablets (2000 mg niacin, 40 mg lovastatin) administered orally under fasting conditions in Treatment = FAST.

Sponsor/Company: Kos Pharmaceuticals, Inc. (Kos)	Individual Study Table	*(For National Authority Use Only)*
Finished Product: Nicostatin™		
Active Ingredients: niacin and lovastatin		

Duration of treatment: Single-dose administration on three separate occasions, each administration separated by at least 10 days

Criteria for evaluation:

Pharmacokinetics:

Pharmacokinetic data were analyzed from all subjects who completed at least one treatment period. Niacin bioequivalence was assessed by NUA maximum plasma concentrations (Cmax) and total urine recovery (niacin and metabolites NUA, MNA, and 2PY) resulting from single-dose administration of 2000 mg niacin. Lovastatin bioequivalence was assessed by plasma lovastatin and supported by lovastatin acid and total HMG-CoA reductase inhibition data resulting from single-dose administration of 40 mg lovastatin.

Safety:

Safety data were summarized and/or analyzed from all subjects who received at least one dose of study medication.

Statistical methods: For pharmacokinetic parameters, classical 90% confidence intervals were calculated for the ratio of least square means from natural log-transformed data. A food effect was concluded when the 90% confidence intervals fell outside ——— % for AUC (or extent of absorption measure) and ——— % for Cmax (absorption rate measure). Adverse events were summarized. No statistical tests were performed on the safety data.

SUMMARY OF RESULTS

Pharmacokinetics:

Mean NUA Cmax was greater for either fed treatment than for FAST, with means of 2.94, 3.96, and 4.40 mcg/mL for FAST, HIGH, and LOW, respectively. Total Recovery of niacin in the urine (as niacin, NUA, MNA, and 2PY) 60.2, 77.3, and 72.7% of the administered niacin dose for FAST, HIGH, and LOW treatments, respectively. A food effect was documented for both HIGH and LOW treatments compared to FAST: niacin bioavailability was significantly lower under fasting conditions. No food effect was documented for the HIGH compared to LOW treatments.

Mean lovastatin Cmax was 9.96, 14.1, and 11.4 ng/mL for FAST, HIGH, and LOW, respectively; mean lovastatin AUClast was 72.9, 49.7, and 51.2 ng*hr/mL for FAST, HIGH, and LOW. Mean lovastatin Tmax was similar for all three treatments: 2.2, 2.1, and 1.8 hr for FAST, HIGH, and LOW, respectively. Lovastatin AUClast data were biased by a second peak, primarily in the FAST treatment, and AUC0-4 was used to evaluate food effects for comparisons to the FAST treatment. Mean AUC0-4 was 23.7, 30.2, and 26.1 ng*hr/mL for FAST, HIGH, and LOW. A food effect was documented in both Cmax and AUC0-4 for the HIGH treatment compared to FAST. A food effect was indeterminate for LOW compared to FAST since only Cmax values were equivalent. Both Cmax and AUClast were equivalent for the HIGH compared to the LOW treatment.

Mean lovastatin acid Cmax was 6.72, 7.83, and 4.73 ng/mL for FAST, HIGH, and LOW, respectively, and mean AUClast was 54.4, 44.4, and 31.2 ng*hr/mL for FAST, HIGH, and LOW. Since lovastatin data were adequate for pharmacokinetic analysis, no conclusions regarding food effects were made from lovastatin acid data.

Mean total HMG-CoA reductase inhibition Cmax was 88.4, 127, and 101 nM-eq for FAST, HIGH, and LOW, respectively, and mean AUClast was 619, 566, and 487 nM-eq*hr for FAST, HIGH, and LOW. Inhibition AUC0-4 was used for food effect comparisons to the FAST treatment. Mean AUC0-4 was 227, 290, and 232 nM-eq*hr for FAST, HIGH, and LOW. A food effect was documented in both Cmax and AUC0-4 for the HIGH treatment compared to FAST. No food effect was documented for LOW compared to FAST; both Cmax and AUC0-4 were equivalent. For HIGH compared to LOW, confidence intervals for Cmax and AUClast were slightly outside the criteria for equivalence, suggesting equivalence and the absence of a food effect.

APPEARS THIS WAY
ON ORIGINAL

Sponsor/Company: Kos Pharmaceuticals, Inc. (Kos)	Individual Study Table	*(For National Authority Use Only)*
Finished Product: Nicostatin™		
Active Ingredients: niacin and lovastatin		

Safety:

One serious adverse event occurred 28 days after the last dose of study medication. The treatment-emergent adverse event reported most frequently for all three treatment groups was flushing.

CONCLUSIONS:

- Niacin bioavailability was significantly greater after a low-fat or a high-fat snack than under fasting conditions.
- Lovastatin bioavailability was significantly greater after a high-fat snack than under fasting conditions based on lovastatin concentrations and total HMG-CoA reductase inhibition.
- A food effect for lovastatin was indeterminate for the comparison of a low-fat snack to fasting. While lovastatin Cmax and total HMG-CoA reductase inhibition Cmax and AUC_{0-t} all suggested equivalence (no food effect), lovastatin AUC_{0-t} was significantly greater in the LOW treatment than the FAST treatment.
- No food effect was documented for either niacin or lovastatin in the comparison between administration after a low-fat and a high-fat snack.
- Nicostatin should be administered after a low-fat snack to enhance niacin and lovastatin bioavailability. Administration under fasting conditions should not be recommended for Nicostatin.
- Study treatments were reasonably well tolerated since the most frequently reported adverse event after any treatment was flushing.

APPEARS THIS WAY
ON ORIGINAL

Table 7 Plasma Niacin and NUA Bioavailability in the Three-Way Crossover Study of the Effect of Food on the Bioavailability of Nicostatin™ Tablets

	Niacin			NUA				
	Mean	SD	%CV	Mean	SD	%CV	Ratio(%) [a]	90% CI
Cmax (mcg/mL)								
Fast	6.37	6.49	102	2.94	1.43	49	High/Fast: 138	122 – 157
High	16.7	11.6	69	3.96	1.53	39	Low/Fast: 155	137 – 175
Low	18.9	10.1	53	4.40	1.38	31	High/Low: 89	79 – 101[†]
AUClast (mcg*hr/mL)								
Fast	16.3	20.5	125	12.4	8.39	68	NA	NA
High	41.6	31.4	75	17.8	7.98	45	NA	NA
Low	50.3	33.1	66	19.5	7.77	40	NA	NA
Tmax (hr)								
Fast	3.3	1.9	59	3.5	1.5	43	High vs Fast: < 0.001* [b]	
High	6.9	1.9	27	7.3	1.6	21	Low vs Fast: < 0.001* [b]	
Low	5.7	1.8	31	6.3	1.8	28	High vs Low: 0.045* [b]	

Niacin dose is 2000 mg in each treatment. N = 26, 26, and 27 for Fast, High, and Low, respectively.
NA = Not Applicable.
Statistically significant at $p \leq 0.05$ level.
[†] Suggests no food effect (i.e., 90% CI for rate of absorption measure within [redacted] %).
[a] Ratio of the least square means of natural-log transformed NUA Cmax for treatments indicated.
[b] p-value by Wilcoxon Signed-Rank Test.
Data Source: Appendices B and G.

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Table 8 Niacin urinary recovery in the Three-Way Crossover Study of the Effect of Food on the Bioavailability of Nicostatin™ Tablets

	Mean	SD	%CV	Ratio(%)[a]		90% CI
Niacin Recovery (% of dose)						
Fast	1.82	1.99	110	NC		NC
High	9.00	6.14	68			
Low	9.04	5.67	63			
NUA Recovery (% of dose)						
Fast	9.75	4.45	46	NC		NC
High	16.5	4.90	30			
Low	17.0	5.28	31			
MNA Recovery (% of dose)						
Fast	13.8	4.21	30	NC		NC
High	17.1	5.67	33			
Low	15.2	3.67	24			
2PY Recovery (% of dose)						
Fast	34.8	7.49	22	NC		NC
High	34.7	8.82	25			
Low	31.5	7.95	25			
Total Recovery[b] (% of dose)						
Fast	60.2	13.6	23	High/Fast:	130	119 – 143
High	77.3	12.5	16	Low/Fast:	122	111 – 133
Low	72.7	12.7	17	High/Low:	107	98 – 117 [†]

Niacin dose is 2000 mg in each treatment. N = 26, 26, and 27 for Fast, High, and Low, respectively.
NC = Not Calculated.
[†] Suggests no food effect (i.e., 90% CI for extent of absorption measure within ——— %).
[a] Ratio of the least square means of natural-log transformed Total Recovery for treatments indicated.
[b] Recovery of niacin, NUA, MNA, and 2PY combined.
Data Source: Appendices F and G.

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Table 9 Plasma Lovastatin Bioavailability in the Three-Way Crossover Study of the Effect of Food on the Bioavailability of Nicostatin™ Tablets

		Mean	SD	%CV	Ratio(%) [a]		90% CI
Cmax (ng/mL)							
	Fast	9.96	7.58	76	High/Fast:	148	130 - 170
	High	14.1	9.38	66	Low/Fast:	121	106 - 138 [†]
	Low	11.4	7.71	67	High/Low:	123	107 - 140 [†]
AUClast (ng*hr/mL)							
	Fast	72.9	62.1	85	High/Fast:	74	66 - 83
	High	49.7	27.9	56	Low/Fast:	76	68 - 85
	Low	51.2	32.2	63	High/Low:	97	87 - 109 [†]
Tmax (hr)							
	Fast	2.2	2.1	94	High vs Fast: 0.573 [b]		
	High	2.1	1.0	47	Low vs Fast: 0.774 [b]		
	Low	1.8	0.6	34	High vs Low: 0.307 [b]		
AUC_{0-t} (ng*hr/mL)							
	Fast	23.7	18.6	78	High/Fast:	140	122 - 160
	High	30.2	17.9	59	Low/Fast:	123	107 - 140
	Low	26.1	15.0	57	High/Low:	Not applicable	
AUCinf (ng*hr/mL)							
	Fast	83.3	68.8	83	NC		NC
	High	50.8	28.0	55	NC		NC
	Low	54.7	36.2	66	NC		NC
k (1/hr)							
	Fast	0.114	0.0601	53	NC		NC
	High	0.250	0.109	44	NC		NC
	Low	0.155	0.0732	47	NC		NC
t1/2 (hr)							
	Fast	6.1 [c]	NC	NC	NC		NC
	High	2.8 [c]	NC	NC	NC		NC
	Low	4.5 [c]	NC	NC	NC		NC

Lovastatin dose is 40 mg in each treatment. N = 26, 26, and 27 for Fast, High, and Low, respectively.
NC = Not Calculated.
* Statistically significant at $p \leq 0.05$ level.
[†] Suggests no food effect (i.e., 90% CI within ——— % for Cmax, ——— % for AUC).
[a] Ratio of the least square means of the natural-log transformed parameter for treatments indicated.
[b] *p*-value by Wilcoxon Signed-Rank Test.
[c] Harmonic mean.
Data Source: Appendices C and G.

Table 10 Plasma Lovastatin Acid Bioavailability in the Three-Way Crossover Study of the Effect of Food on the Bioavailability of Nicostatin™ Tablets

		Mean	SD	%CV	Ratio(%) [a]		90% CI
Cmax (ng/mL)							
	Fast	6.72	5.28	79	High/Fast:	121	102 – 144
	High	7.83	5.56	71	Low/Fast:	76	64 – 90
	Low	4.73	2.56	54	High/Low:	160	135 – 191
AUClast (ng*hr/mL)							
	Fast	54.4	43.5	80	High/Fast:	85	74 – 98
	High	44.4	31.3	71	Low/Fast:	61	53 – 71
	Low	31.2	17.7	57	High/Low:	139	120 – 161
Tmax (hr)							
	Fast	4.7	1.9	42	High vs Fast: 0.259 [b]		
	High	4.0	1.2	29	Low vs Fast: 0.196 [b]		
	Low	3.9	1.6	42	High vs Low: 0.595 [b]		
AUCinf (ng*hr/mL)							
	Fast	60.5	46.1	76	NC		NC
	High	46.0	31.9	69	NC		NC
	Low	32.9	17.8	54	NC		NC
k (1/hr)							
	Fast	0.134	0.0825	61	NC		NC
	High	0.276	0.108	39	NC		NC
	Low	0.199	0.0901	45	NC		NC
t1/2 (hr)							
	Fast	5.2 [c]	NC	NC	NC		NC
	High	2.5 [c]	NC	NC	NC		NC
	Low	3.5 [c]	NC	NC	NC		NC

Lovastatin dose is 40 mg in each treatment. N = 26, 26, and 27 for Fast, High, and Low, respectively.
NC = Not Calculated.
Statistically significant at $p \leq 0.05$ level.
[†] Suggests no food effect (i.e., 90% CI within [redacted]% for Cmax, [redacted]% for AUC).
[a] Ratio of the least square means of the natural-log transformed parameter for treatments indicated.
[b] p-value by Wilcoxon Signed-Rank Test.
[c] Harmonic mean.
Data Source: Appendices C and G.

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Table 11 Plasma Total HMG-CoA Reductase Inhibition Bioavailability in the Three-Way Crossover Study of the Effect of Food on the Bioavailability of Nicostatin™ Tablets

		Mean	SD	%CV	Ratio(%) [a]		90% CI
Cmax (nM-eq)							
	Fast	88.4	50.2	57	High/Fast:	153	137 - 172
	High	127	53.8	42	Low/Fast:	119	106 - 134 †
	Low	101	47.7	47	High/Low:	129	115 - 145
AUClast (nM-eq*hr)							
	Fast	619	343	55	High/Fast:	96	88 - 104 †
	High	566	225	40	Low/Fast:	81	75 - 88
	Low	487	213	44	High/Low:	118	109 - 128
Tmax (hr)							
	Fast	2.0	1.4	70	High vs Fast: 0.075 [b]		
	High	2.3	1.1	49	Low vs Fast: 0.141 [b]		
	Low	2.2	0.8	38	High vs Low: > 0.999 [b]		
AUC_{0-t} (nM-eq*hr)							
	Fast	227	115	51	High/Fast:	134	120 - 150
	High	290	123	43	Low/Fast:	108	97 - 121 †
	Low	232	97.6	42	High/Low:	Not applicable	
AUCinf (nM-eq*hr)							
	Fast	677	374	55	NC		NC
	High	585	225	39	NC		NC
	Low	507	219	43	NC		NC
k (1/hr)							
	Fast	0.125	0.0550	44	NC		NC
	High	0.213	0.0734	34	NC		NC
	Low	0.185	0.0787	43	NC		NC
t1/2 (hr)							
	Fast	5.5 [c]	NC	NC	NC		NC
	High	3.3 [c]	NC	NC	NC		NC
	Low	3.8 [c]	NC	NC	NC		NC

Lovastatin dose is 40 mg in each treatment. N = 26, 26, and 27 for Fast, High, and Low, respectively.
NC = Not Calculated.
* Statistically significant at $p \leq 0.05$ level.
† Suggests no food effect (i.e., 90% CI within ——— % for Cmax, ——— % for AUC).
[a] Ratio of the least square means of the natural-log transformed parameter for treatments indicated.
[b] p-value by Wilcoxon Signed-Rank Test.
[c] Harmonic mean.
Data Source: Appendices C and G.

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