CENTER FOR DRUG EVALUATION AND RESEARCH

APPLICATION NUMBER: 21-249

STATISTICAL REVIEW(S)

STATISTICAL REVIEW AND EVALUATION
CLINICAL STUDIES

NDA #: 21-249
Drug: Nicostatin (niacin ER + lovastatin in a single tablet)
Sponsor: Kos Pharmaceuticals
Indication: Lipid lowering
Date of Submission: September 21, 2000
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Keywords: clinical studies, NDA review, drop-outs, combination drug

Introduction

Nicostatin is a combination tablet of niaspan (as an extended release —— and lovastatin /————). The sponsor has submitted the results of two clinical trials and one long-term study (MA-98-010407) to establish the efficacy of Nicostatin. Table 1 gives a brief summary of the two trials reviewed here.

Table 1. Summary of Double-Blind, Randomized, Controlled Clinical Trials for Nicostatin

Study	# of Sites	Treatment Arms Starting dose⇒Ending dose (ITT N)	Duration of Treatment
MA-98-010406 (4/99-3/00)	23	Niaspan 500⇒2000 (56) Nicostatin 500/20⇒1000/20 (55) Nicostatin 500/20⇒2000/40 (52) Lovastatin 20⇒40 (59)	28 weeks (Minimum of 4 weeks at each dose level)
MA-98-010414 (5/99-2/00)	16	Niaspan 500⇒2500 (28) Nicostatin 500/10⇒2500/10 (32) Nicostatin 500/20⇒2500/20 (33) Nicostatin 500/40⇒2500/40 (29) Lovastatin 10⇒40 (31)	20 weeks (Minimum of 4 weeks at each dose level)

The long-term study (MA-98-010407) is not reviewed here because there is no comparative data provided by that study. It is an open-label 2-year on-going study with one treatment group. All patients start with Nicostatin 500/10 and are titrated to 2000/40. A total of 814 patients entered the trial; 226 completed one year at the time of the submission. About ⅓ of the patients discontinued treatment. See the medical review for the results of this study.

Potential Indications

There are two potential indications for the use of this combination therapy: 1) as a **convenience product** for patients presenting with low HDL, high triglycerides (TG) and high LDL , or 2) as **first line therapy for LDL lowering.** For a full explanation of the clinical use of this product under these two indications, see the medical review.

As a convenience product, each component of the combination product is assumed to make a unique and separate contribution to efficacy of the combination. For Nicostatin, niaspan primarily provides HDL raising and TG lowering while lovastatin primarily provides LDL lowering. To establish the efficacy of Nicostatin as a convenience product, the sponsor would need to show that Nicostatin is superior to niaspan alone for LDL lowering (this comparison measures the contribution of lovastatin) and that Nicostatin is superior to lovastatin alone for HDL raising and TG lowering (this comparison measures the contribution of niaspan).

As first line therapy for LDL lowering, each component of the combination is assumed to contribute to the lowering of LDL. The combination, then, would need to be more efficacious than lovastatin alone and niaspan alone for LDL lowering.

With this NDA, the sponsor intended to show that Nicostatin is effective as a first -line therapy for LDL lowering.

Nicostatin Doses

Nicostatin like niaspan must be titrated. In both clinical studies, Nicostatin and niaspan are increased monthly starting at a minimum dose of 500 mg of niaspan and increasing to a maximum of 2000 mg (Study 406) or 2500 mg (Study 414). The titration schemes used for the highest doses studied are shown in Table 2 below. Also shown in this table is the maximum titration scheme recommended in the label. The titration used in Study 414 follows the proposed labeling while the titration in Study 406 is more protracted.

Table 2. Maximum titration schemes used in the clinical trials and recommended in the proposed labeling

Treatment Group	WEEK						
	1-4	5-8	9-12	13-16	17-20	21-24	25-28
Study 406 NIC 2000/40	500/20	750/20	1000/20	1000/40	1500/40	2000/40	2000/40
Study 414 NIC 2500/40	500/40	1000/40	1500/40	2000/40	2500/40	NA	NA
Titration for NIC Rec. by Label	500/20	1000/20 1000/40	1500/20 1500/40	2000/20 2000/40			

The sponsor has stated in the Integrated Summary of Efficacy of this NDA that doses of 500/20 to 2000/40 are effective at lowering LDL. The sponsor's proposed labeling recommends maintenance doses of 500/20 to 2000/40 and states that tablets in strengths of 500/20, 750/20 and 1000/20 will be manufactured. From the NDA, the study designs and the proposed labeling, it appears that the sponsor intends to show the following doses to be efficacious: **500/20, 750/20, 1000/20, 1000/40, 1500/40, 2000/40**. This reviewer will test these combinations and also those additional combinations which may be assessed according to the designs of the studies.

Sponsor's Statistical Analysis Plans

The primary efficacy endpoint for both trials was percent change from baseline in LDL. The intent-to-treat population was defined as all patients who have received at least one dose of study drug; however all of the sponsor's analyses were performed on the available data only (observed cases). For the primary comparisons, an ANOVA with treatment and center as main effects was planned. The interaction of treatment and center was assessed first and, if non-significant ($p<.05$), it was not included in the ANOVA model. In addition to primary comparisons (these are described below with the review of each study), the sponsor planned to perform many secondary comparisons (both within and between treatment groups at multiple visits).

Reviewer's Methods

To assess the efficacy of Nicostatin, this reviewer addressed both potential indications. To establish the efficacy of Nicostatin as a convenience product, the following 3 hypotheses were tested:

For LDL: $H_o: E_{NL} = E_N$ versus $H_a: E_{NL} \mid E_N$
For HDL: $H_o: E_{NL} = E_L$ versus $H_a: E_{NL} \mid E_L$
For TG: $H_o: E_{NL} = E_L$ versus $H_a: E_{NL} \mid E_L$

To establish the efficacy of Nicostatin as first-line therapy for LDL lowering, the following 2 hypotheses were tested:

For LDL: $H_o: E_{NL} = E_N$ versus $H_a: E_{NL} \mid E_N$
$H_o: E_{NL} = E_L$ versus $H_a: E_{NL} \mid E_L$

Where E=% change from baseline, NL=Nicostatin (niaspan+lovastatin), N=niaspan and L=lovastatin.

The hypotheses for each indication are all tested under .05 level of significance; no adjustment of p-values is needed since all null hypotheses for each indication must be rejected in order to establish the efficacy of Nicostatin.

The major difference between the 2 approaches is the need to show the contribution of niaspan to LDL lowering (the last hypothesis shown above) in order to establish the efficacy of Nicostatin as first-line therapy for LDL lowering. Note that the contribution of niaspan is shown by comparing the combination to lovastatin alone. So lack of a statistically significant difference between Nicostatin and lovastatin for LDL indicates that the LDL lowering is due to lovastatin alone.

To test these hypotheses, an ANOVA with treatment and center as terms was performed. Tests of treatment by center interactions were performed and are noted in this review when significant. Analyses with the appropriate baseline were also done and shown to produce similar results. An intent-to-treat (ITT) sample with the last observation carried forward (LOCF) was used.

A total of 16 doses of Nicostatin were administered in the two trials; each for a minimum of 4 weeks (4 weeks is considered sufficient for showing response). As mentioned above, only 6 of these 16 doses will be promoted by the sponsor. This reviewer looked at all doses that could be compared to each of its components. For this reviewer, in order to test a dose of Nicostatin, two criteria must be met:

1. The week of assessment must be the same for the Nicostatin dose and its components.
2. The comparisons should be between randomized groups.

Comparisons within groups and between different timepoints may produce biased results. Some factors that may bias the latter include the presence of dropouts, carryover of effects and impact of factors usually controlled by randomization. Note that the sponsor has performed analyses within groups and across timepoints; this reviewer considers none of those analyses acceptable (a point that was made to the sponsor at the IND stage of this application).

Study MA-98-010406 (conducted 4/99 to 3/00)

Study MA-98-010406 (referred to as Study 406, henceforth) is a double-blind, randomized, controlled, parallel study. Following at least 4 weeks on the NCEP Step 1 diet and on no lipid-lowering medications, two consecutive (within 7-10 days of each other) lipid profiles were performed to assess qualification for randomization. Patients were required to meet NCEP guidelines for treatment for elevated LDL and were to have triglycerides $\leq$800 mg/dL.

Patients satisfying entry criteria were randomized to one of 4 treatment groups (2 Nicostatin groups (NIC), one niaspan group (NIA) and one lovastatin group (LOVA); the treatment schedule for each of these groups is shown in Table 3 below. In this trial patients reach their maximum dose at Week 21 while in practice one could reach maximal dose after 13 weeks if titrated as recommended in the Nicostatin label. The latter may have implications regarding interpretation of the safety data from this trial.

Table 3. Study 406 Titration schedule by treatment group and week

Treatment	WEEK						
Group	1-4	5-8	9-12	13-16	17-20	21-24	25-28
NIC 1000/20	500/20	750/20	1000/20	1000/20	1000/20	1000/20	1000/20
NIC 2000/40	500/20	750/20	1000/20	1000/40	1500/40	2000/40	2000/40
NIA 2000	500	750	1000	1000	1500	2000	2000
LOVA 40	20	20	20	40	40	40	40

Given the design and this reviewer's criteria for making comparisons, a comparison can be made at the end of each 4 week period. All the doses of Nicostatin administered in this trial are proposed for marketing.

Patient disposition

A total of 499 patients were screened at 23 USA centers; 237 were randomized, 1 patient never took any medication and is not included in the ITT population. The ITT population includes those patients having at least one dose of medication and at least one primary efficacy (LDL) observation on therapy.

The dropout rates are notably higher in the groups administered niaspan alone or in combination compared to the lovastatin group alone (Table 4). Almost 20% of the combination therapy patients drop out after only 3 months of therapy; nearly 30% do not complete the trial. Only 13% drop out of the lovastatin arm.

Table 4. Study 406 Patient disposition

Week Completed	NIC 1000/20	NIC 2000/40	NIA 2000	LOVA 40
Randomized	57 (100%)	57 (100%)	61 (100%)	61 (100%)
Baseline	57 (100%)	57 (100%)	61 (100%)	61 (100%)
Week 4	55 (96%)	52 (91%)	56 (92%)	59 (97%)
Week 8	49 (86%)	48 (84%)	51 (84%)	58 (95%)
Week 12	48 (84%)	47 (82%)	47 (77%)	56 (92%)
Week 16	43 (75%)	45 (79%)	44 (72%)	56 (92%)
Week 20	42 (74%)	42 (74%)	43 (70%)	54 (89%)
Week 24	42 (74%)	42 (74%)	42 (69%)	53 (87%)
Week 28	40 (70%)	42 (74%)	41 (67%)	53 (87%)
ITT	55 (96%)	52 (91%)	56 (92%)	59 (97%)

Table 5 shows the reasons patients discontinued medication by treatment group. In all groups the primary reason for discontinuation was an adverse event. In the lovastatin group, the most common ADE was muscle aches (4 of the 5). Flushing was the most common ADE in the combination groups; in the niaspan alone group, the most common ADE was itching (rash, hives, pruritus) with flushing second.

Table 5. Study 406 Reasons for discontinuation

Reason	NIC 1000/20 (n=57)	NIC 2000/40 (n=57)	NIA 2000 (n=61)	LOVA 40 (n=61)
ADE / not flushing	6 (11%)	4 (7%)	9 (15%)	5 (8%)
ADE / flushing	6 (11%)	6 (11%)	3 (5%)	1 (2%)
Patient withdrew	1 (2%)	1 (2%)	2 (3%)	0 (0%)
Lost-to-follow-up	1 (2%)	0 (0%)	2 (3%)	0 (0%)
Protocol violation	2 (4%)	2 (4%)	2 (3%)	1 (2%)
Other	1 (2%)	2 (4%)	2 (3%)	1 (2%)
Total	17 (30%)	15 (26%)	20 (33%)	8 (13%)

Most of the flushing occurred during the first three months of therapy. Of the 12 Nicostatin/niaspan patients who discontinued before Week 4 (the first visit), six patients reported flushing or itching.

Baseline demographics

The treatment groups were generally well-balanced by baseline characteristics (Table 6) with two exceptions; more males and more elderly in the lovastatin group.

Patients ranged in age from 32 to 86 years with a mean of about 59 years; about ⅓ of the patients were 65 or older. The majority of patients were Caucasian (87%), non-diabetics (~87%), and non-smokers (85%).

Table 6. Study 406 Baseline characteristics

	NIC 1000/20 (n=57)	**NIC 2000/40 (n=57)**	**NIA 2000 (n=61)**	**LOVA 40 (n=61)**
Age (years)				
Mean (SD)	59 (12)	59 (12)	58 (11)	61 (10)
Range	32-86	35-84	33-84	33-81
%≥65 years	32%	35%	28%	41%
Gender				
% Males/females	54%/46%	56%/44%	46%/54%	64%/36%
Race				
% Caucasian	88%	86%	90%	84%
% Black	4%	7%	5%	5%
% Hispanic	9%	5%	3%	7%
% Asian	0%	2%	2%	5%
BMI (kg/m^2)				
Mean (SD)	30 (4)	29 (5)	29 (5)	29 (7)
Range	23-45	18-50	22-45	18-58

Efficacy Results

According to the protocol. the primary objectives of this trial are to compare NS1000/20 to LOVA20 at Week 12 and NS1000/20 to NS2000/40 at Week 28 for **LDL**

response. Several other comparisons were listed as secondary comparisons. At the IND stage, the sponsor was advised by FDA statisticians to perform the standard combination therapy comparisons, i.e. the combination versus each component as the primary analyses. The focus of this review is on the latter, not the sponsor's protocol defined comparisons.

Results from tests of all hypotheses to support both indications are presented in Table 7. For analyses of the 3 lowest doses (500/20, 750/20 and 1000/20), the Nicostatin arms were combined. This is acceptable given the design (see Table 3 on page 5).

Table 7. ITT (LOCF) lipoprotein responses[1] for Nicostatin doses in Study 406

	Nicostatin Mean (SD)	Niaspan Mean (SD)	Lovastatin Mean (SD)	NIC Vs NIA p-value	NIC Vs LOVA p-value
Dose	500/20	500	20		
N	106	56	59		
Week 4					
LDL%change	-29% (11)	-0.5% (11)	-26% (10)	.0001	.13
HDL%change	+11% (11)	+5% (11)	+6% (10)	.007	.005
TG%change	-16% (32)	-8% (29)	-16% (23)	.15	.89
Dose	750/20	750	20		
N	106	56	59		
Week 8					
LDL%change	-29% (12)	-1% (12)	-27% (10)	.0001	.52
HDL%change	+14% (14)	+6% (14)	+3% (12)	.002	.0001
TG%change	-21% (30)	-5% (37)	-16% (28)	.002	.26
Dose	1000/20	1000	20		
N	106	55	59		
Week 12					
LDL%change	-30% (13)	-3% (12)	-29% (9)	.0001	.49
HDL%change	+19% (15)	+12% (14)	+3% (10)	.001	.0001
TG%change	-26% (28)	-13% (33)	-15% (26)	.01	.01
Dose	1000/40	1000	40		
N	52	56	59		
Week 16					
LDL%change	-35% (13)	-5% (13)	-31% (10)	.0001	.06
HDL%change	+19% (14)	+12% (16)	+5% (11)	.02	.0001
TG%change	-32% (30)	-18% (27)	-15% (23)	.04	.01
Dose	1500/40	1500	40		
N	52	56	59		
Week 20					
LDL%change	-36% (16)	-10% (13)	-32.5% (10)	.0001	.20
HDL%change	+26% (15)	+18% (19)	+5% (12)	.007	.0001
TG%change	-37% (32)	-22% (31)	-18% (22)	.01	.0006
Dose	2000/40	2000	40		
N	52	56	59		
Week 24					
LDL%change	-37% (18)	-11% (15)	-31% (10)	.0001	.04
HDL%change	+28% (18)	+20% (17)	+5% (12)	.006	.0001
TG%change	-43% (27)	-30% (26)	-16% (23)	.11	.0007
Dose	2000/40	2000	40		
N	52	56	59		
Week 28					
LDL%change	-40% (14)	-10% (15)	-31% (11)	.0001	.002
HDL%change	+28% (17)	+19% (21)	+6% (15)	.0008	.0001
TG%change	-40% (27)	-20% (32)	-20% (22)	.004	.0002

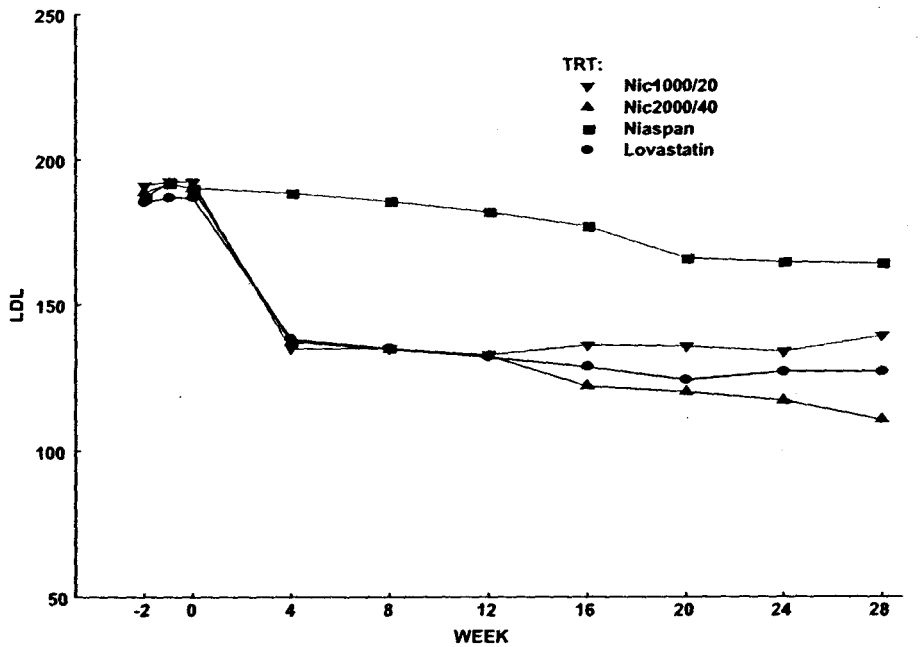
[1] All results are from ANOVA with treatment and center as terms. TG was also analyzed using a Wilcoxon rank sum test; those results are reported if they differed from the ANOVA results.

All Nicostatin doses beat niaspan alone for LDL (Table 7). The comparisons of Nicostatin to lovastatin for LDL show no statistically significant difference between lovastatin and Nicostatin doses 500/20, 750/20, 1000/20, 1000/40 and 1500/40; so these doses of Nicostatin do not offer an advantage over lovastatin alone. The highest dose of Nicostatin, 2000/40, was statistically different from lovastatin 40 (p=.002) with decreases of –40% and –31%, respectively. Therefore, only the 2000/40 dose supports a LDL lowering indication.

The HDL results show that Nicostatin is more effective at increasing HDL than either component for all dose combinations. Also, Nicostatin significantly drops triglycerides compared to lovastatin for doses of the niaspan component 1000 mg or greater. The HDL, LDL and TG results suggest that doses of Nicostatin of 1000/20 and greater satisfy statistical criteria for showing Nicostatin to be an acceptable convenience product.

To see how each treatment group performs over time for patients on study (observed cases), the responses are illustrated in Figure 1 below for LDL and in Appendix 1 for % change of LDL, HDL, TG and Lp(a). The largest LDL response for Nicostatin is seen after 4 weeks on therapy; this response is clearly due to the lovastatin component. Up until 12 weeks of therapy (niaspan 500, 750 and 1000), it is clear that the niaspan component does not contribute to the LDL response.

Figure 1. Study 406 LDL by week and treatment group (observed cases)



Dose by week on study

Treatment Group	WEEK						
	1-4	5-8	9-12	13-16	17-20	21-24	25-28
NIC 1000/20 ▼	500/20	750/20	1000/20	1000/20	1000/20	1000/20	1000/20
NIC 2000/40 ▲	500/20	750/20	1000/20	1000/40	1500/40	2000/40	2000/40
NIA 2000 ■	500	750	1000	1000	1500	2000	2000

LOVA 40 ●	20	20	20	40	40	40	40

From Appendix 1, the responses for HDL and TG are as expected for the four treatment groups, with dose-related changes seen for Nicostatin and niaspan. The Lp(a) results show increases for lovastatin and decreases for niaspan and Nicostatin with the largest decreases seen for niaspan alone.

In all graphs of the longitudinal LDL data, doubling of the lovastatin dose from 20 mg to 40 mg has a small effect on response; about 50% of the patients have a further decrease in LDL of 2% or less comparing Week 12 and Week 16 (for Nicostatin the median decrease is 5% when increasing the dose from 1000/20 to 1000/40). This small change when doubling the dose is less than what might be expected from the label of lovastatin; however, the Lovastatin 40 mg mean decrease for LDL of 32% is consistent with labeling (see Table 14 of this review).

The graphical data of observed cases is consistent with the LOCF results presented in Table 7 suggesting that dropouts did not have a significant impact on interpretation of the outcome. The differential dropout rates seen for lovastatin and Nicostatin 2000/40, however, invite further examination of the comparison of 2000/40 to lovastatin 40 using both the completer data and the LOCF data. Again the results are similar (Table 8).

Table 8. Reviewer's Week 28 results for Nicostatin 2000/40, niaspan 2000 and lovastatin 40

	NIC 2000/40 Mean (SD)	**NIA 2000 Mean (SD)**	**LOVA 40 Mean (SD)**	**NIC vs NIA p-value**	**NIC vs LOVA p-value**
Sample Size					
OC	42	41	53		
LOCF	52	56	59		
LDL					
Baseline	190 (33)	190 (32)	187 (36)	.86	.62
Week 28					
OC	-42% (14)	-13% (16)	-32% (11)	.0001	.002
LOCF	-40% (14)	-10% (15)	-31% (11)	.0001	.002
HDL					
Baseline	45 (13)	47 (11)	44 (11)	.51	.33
Week 28					
OC	+30% (17)	+16% (19)	+6% (15)	.01	.0001
LOCF	+28% (17)	+19% (21)	+6% (15)	.001	.0001
TG (median)					
Baseline	187	180	167	.20	.14
Week 28					
OC	-44%	-31%	-20%	.002	.0001
LOCF	-43%	-25%	-20%	.0002	.0001
Lp (a)					
Baseline	36 (37)	43 (41)	43 (42)	.29	.22
Week 28					
OC	-19% (25)	-24% (25)	-2% (30)	.31	.003
LOCF	-15% (27)	-22% (23)	-2% (29)	.17	.01

An analysis of LDL which considers the impact of dropouts further was performed by this reviewer. The analysis called ETRANK developed by Entsuah (J. Biopharm. Stat., 6(4), 457-475, 1996) is a non-parametric procedure which uses all the observed longitudinal data and makes adjustments to the analysis for treatment-related dropouts. This reviewer found no difference between results of an endpoint (LOCF) analysis and results of the ETRANK analysis. Both analyses showed a significant difference between Nicostatin 2000/40 and lovastatin 40 for LDL.

Reviewer's Comments on Study 406

The results from Study 406 showed the following:

1. Statistically significant lowering of LDL for Nicostatin 2000/40 compared to lovastatin 40 mg alone and niaspan 2000 mg alone. Only this Nicostatin dose was shown to provide a significant benefit regarding LDL lowering over lovastatin alone. So only the results for the 2000/40 dose support a primary indication of LDL lowering.
2. All doses of Nicostatin of 1000/20 or greater show significant lowering of LDL compared to niaspan (i.e. significant lovastatin contribution) and significant lowering of TG with significant raising of HDL compared to lovastatin (i.e. significant niaspan contribution). Therefore the results for doses of 1000/20 or greater support Nicostatin as a convenience product.
3. Twice as many patients dropped out in the Nicostatin arms as in the lovastatin arm, primarily for treatment related reasons. No analyses performed by this reviewer showed quantitatively the impact of discontinuing on outcome; nevertheless, the impact is still substantial given that nearly ⅓ of patients cannot tolerate Nicostatin. This is particularly an important issue when considering LDL lowering alone. Patients would clearly gain greater benefit from titration of lovastatin alone to optimal effect without risking intolerability to niaspan.

Study MA-98-010414 (conducted 5/99 to 2/00)

Study MA-98-010414 (referred to as Study 414, henceforth) is a double-blind, randomized, controlled, parallel study. Following at least 4 weeks on the NCEP Step 1 diet and on no lipid-lowering medications, two consecutive (within 7-10 days of each other) lipid profiles were performed to assess qualification for randomization. Patients were required to meet NCEP guidelines for treatment for elevated LDL and were to have triglycerides≤800 mg/dL.

Patients satisfying entry criteria were randomized to one of 5 treatment groups (3 Nicostatin groups (NIC), one niaspan group (NIA) and one lovastatin group (LOVA); the treatment schedule for each of these groups is shown in Table 9 below.

Table 9. Study 414 Titration schedule by treatment group and week

Treatment Group	Week				
	1-4	5-8	9-12	13-16	17-20
NS 2500/10	**500/10**	**1000/10**	1500/10	2000/10	2500/10
NS 2500/20	500/20	1000/20	**1500/20**	**2000/20**	2500/20
NS 2500/40	500/40	1000/40	1500/40	2000/40	**2500/40**
NIA 2500	**500**	**1000**	**1500**	**2000**	**2500**
LOVA 40	**10**	**10**	**20**	**20**	**40**

Given the design and this reviewer's criteria for making comparisons (see page 4), comparisons of the bolded doses may be made. **None** of the bolded combinations are proposed by the sponsor for marketing. Nevertheless, this reviewer examined the results for these doses of Nicostatin.

Patient disposition

A total of 299 patients were screened at 16 USA centers; 164 were randomized (Table 10). The dropout rates are highest for niaspan alone and the 2500/20 and 2500/40 Nicostatin groups with less than ¾ of the patients completing the study. Interestingly, the retention rates in the NIC 2500/10 and lovastatin arms are the same at 88%. Most dropouts occur during the first 8 weeks of the study.

Table 10. Study 414 Patient disposition

Week Completed	NIC 2500/10	NIC 2500/20	NIC 2500/40	NIA 2500	LOVA 40
Randomized	34 (100%)	34 (100%)	32 (100%)	31 (100%)	33 (100%)
Baseline	34 (100%)	34 (100%)	32 (100%)	31 (100%)	33 (100%)
Week 4	32 (94%)	33 (97%)	29 (91%)	28 (90%)	31 (94%)
Week 8	32 (94%)	30 (88%)	27 (84%)	27 (87%)	30 (91%)
Week 12	31 (91%)	26 (76%)	23 (72%)	26 (84%)	29 (88%)
Week 16	30 (88%)	26 (76%)	23 (72%)	25 (81%)	29 (88%)
Week 20	30 (88%)	24 (71%)	23 (72%)	23 (74%)	29 (88%)
ITT	32 (94%)	33 (97%)	29 (91%)	28 (90%)	31 (94%)

Intent-to treat in the above table is defined as those patients having at least one dose of medication and at least one primary efficacy (LDL) observation on therapy.

Table 11 shows the reasons patients discontinued medication by treatment group. In all groups, the primary reason for discontinuation was an adverse event. In the

niaspan group, ADE's (other than flushing) included vomiting, diarrhea, nausea and rash. In the Nicostatin groups, rash was the most common non-flushing ADE (9 of the 16 ADE's); all occurred after at least 4 weeks on therapy. The absence of dropouts due to flushing in the NIC 2500/10 group is curious. Further examination of the flushing data showed that about 60% of the patients receiving NIC 2500/20, NIC 2500/40 and NIA 2500, 50% of NIC 2500/10 patients and 16% of the lovastatin patients experienced flushing at some time during the trial. Given the small number of patients of this trial, this variability in flushing between the 2500/10 dose and the other Nicostatin doses is not unexpected.

Table 11. Study 414 Reasons for discontinuation

Reason	NIC 2500/10 (n=34)	NIC 2500/20 (n=34)	NIC 2500/40 (n=32)	NIA 2500 (n=31)	LOVA 40 (n=33)
ADE / not flushing	2 (6%)	5 (15%)	5 (16%)	4 (13%)	3 (9%)
ADE / flushing	0	4 (12%)	2 (6%)	3 (10%)	0
Patient withdrew	0	0	0	0	1 (3%)
Lost-to-follow-up	0	1 (3%)	0	0	0
Protocol violation	2 (6%)	0	1 (3%)	1 (3%)	0
Other	0	0	1 (3%)	0	0
Total	4 (12%)	10 (29%)	9 (28%)	8 (26%)	4 (12%)

Baseline demographics

The treatment groups were generally well-balanced for baseline characteristics (Table 12) with the exception of percentage of patients 65 years or older. In the Nicostatin groups, about 45% are 65 or older while in the niaspan and lovastatin groups the percentages are 21% and 35%, respectively.

Patients ranged in age from 28 to 78 years with a mean of about 59 years. The majority of patients were Caucasian (82%), non-diabetics (91%), and non-smokers (84%).

Table 12. Study 414 Baseline characteristics

Reason	NIC 2500/10 (n=34)	NIC 2500/20 (n=34)	NIC 2500/40 (n=32)	NIA 2500 (n=31)	LOVA 40 (n=33)
Age (years)					
Mean (SD)	59 (11)	61 (10)	60 (11)	58 (11)	58 (14)
Range	35-74	38-75	31-78	35-78	28-78
%≥65 years	44%	45%	45%	21%	35%
Gender					
% Males/females	50%/50%	53%/47%	47%/53%	55%/45%	55%/45%
Race					
% Caucasian	85%	74%	84%	80%	88%
% Black	15%	21%	13%	10%	9%
% Hispanic	0	0	0	3%	0
% Asian	0	6%	3%	6%	3%
BMI (kg/m^2)					
Mean (SD)	29 (5)	28 (5)	30 (8)	30 (8)	28 (4)
Range	11-45	19-46	13-55	21-57	23-36

Efficacy Results

According to the protocol, the primary objectives of this trial were to compare Nicostatin1500/20 to lovastatin 20 (Week 12) and Nicostatin 2000/40 to lovastatin 40 for LDL response. The latter comparison involves data from two different time points (Weeks 16 and 20); this reviewer does not think that the latter comparison is appropriate for reasons stated earlier in this review (see page 4). Several other comparisons were listed as additional secondary comparisons by the sponsor.

Results for analyses performed by this reviewer are provided in Table 13 below.

Table 13. ITT (LOCF) lipoprotein responses[1] for Nicostatin doses in Study 414

	Nicostatin Mean (SD)	Niaspan Mean (SD)	Lovastatin Mean (SD)	NIC vs NIA p-value	NIC vs LOVA p-value
Dose	500/10	500	10		
N	32	28	31		
Week 4					
LDL%change	-22% (10)	-3% (7)	-19% (11)	.0001	.29
HDL%change	+9% (11)	+3% (7)	+6% (8)	.04	.20
TG%change	-10% (32)	-2% (26)	-2% (38)	.15	.89
Dose	1000/10	1000	10		
N	32	28	31		
Week 8					
LDL%change	-25% (10)	-7% (10)	-20% (9)	.0001	.10
HDL%change	+18% (18)	+9% (11)	+5% (15)	.02	.0001
TG%change	-14% (36)	-10% (26)	+2% (41)	.76	.03
Dose	1500/20	1500	20		
N	33	28	31		
Week 12					
LDL%change	-34% (17)	-11% (13)	-23% (11)	.0001	.001
HDL%change	+23% (16)	+18% (18)	+6% (13)	.28	.0001
TG%change	-31% (28)	-16% (44)	-16% (26)	.15	.03
Dose	2000/20	2000	20		
N	33	28	31		
Week 16					
LDL%change	-37% (17)	-14% (14)	-22% (14)	.0001	.0001
HDL%change	+24% (20)	+27% (20)	+7% (12)	.62	.0001
TG%change	-33% (32)	-26% (32)	+2% (42)	.0001	.0001
Dose	2500/40	2500	40		
N	29	28	31		
Week 20					
LDL%change	-43% (22)	-17% (18)	-25% (13)	.0001	.0001
HDL%change	+29% (21)	+30% (18)	+9% (11)	.49	.0001
TG%change	-44% (31)	-41% (23)	-9% (33)	.73	.0001

The results for NIC1000/10 support an indication for convenience therapy, the results for the three higher doses of Nicostatin (1500/20, 2000/20 and 2500/40) support both potential indications; convenience therapy and LDL lowering. However, **none** of these doses have been proposed for marketing according to the sponsor's label.

A statistically significant treatment by center interaction ($p<.13$) was measured when analyzing the LDL data (both LOCF and OC data). An exploratory analysis by this reviewer revealed the interaction was primarily due to Center 7; exclusion of Center 7

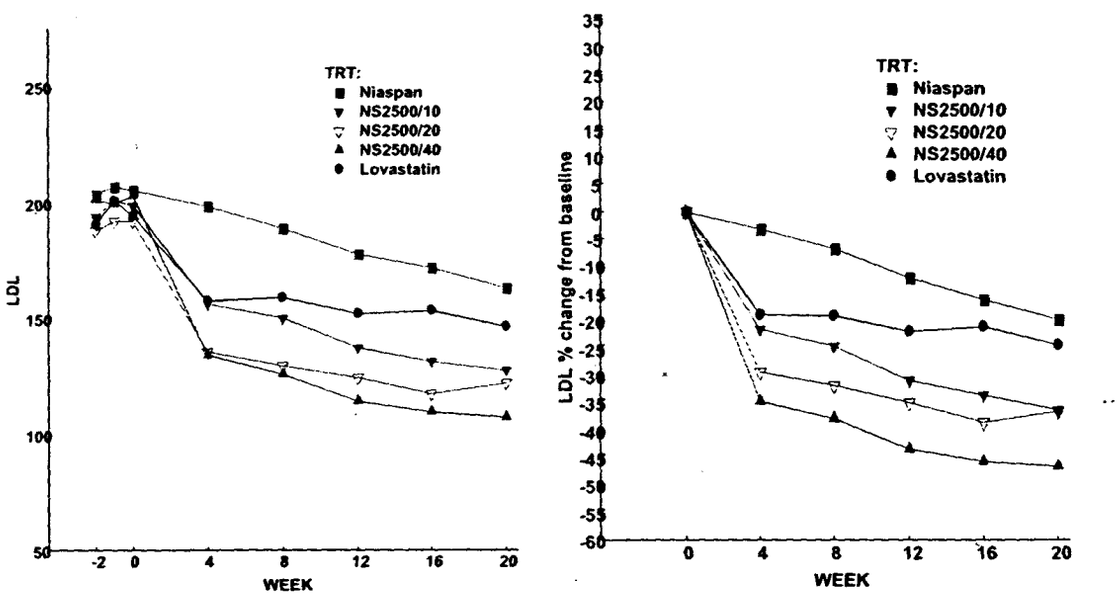
[1] All results are from ANOVA with treatment and center as terms. TG was also analyzed using a Wilcoxon rank sum test; those results are reported if they differed from the ANOVA results.

increased the interaction p-value to ~.45. The exclusion of Center 7 data did not appreciably change the results reported above.

The results over time (Figure 2) show a steady decline in mean LDL for the Nicostatin arms and the niaspan arm but only small changes after Week 4 in the lovastatin arm. The lack of additional response with doubling of the dose of lovastatin from 10 to 20 and 20 to 40 concerned FDA; particularly since the contribution of lovastatin to Nicostatin was evident at each time point comparing across the Nicostatin arms. Doubling of lovastatin from 20 mg to 40 mg resulted in a mean additional lowering of about 2% while titrating Nicostatin from 1000/20 to 1000/40 resulted in a mean additional decrease of about 6% (results similar to those seen in Study —).

Figure 2. Study 414 LDL by week and treatment group (observed cases)

LDL mg/dl **LDL % change from baseline**



Dose Titration in Study 414

Treatment Group	WEEK				
	1-4	5-8	9-12	13-16	17-20
NIA 2500 ■	500	1000	1500	2000	2500
NS 2500/10 ▼	500/10	1000/10	1500/10	2000/10	2500/10
NS 2500/20 ⊕	500/20	1000/20	1500/20	2000/20	2500/20
NS 2500/40 ▲	500/40	1000/40	1500/40	2000/40	2500/40
LOVA 40 ●	10	10	20	20	40

To determine if the lovastatin 40 mg response of ~24% is consistent with historical data, this reviewer compiled results reported in the lovastatin label and in additional studies reviewed by FDA (Table 14). It is clear that the decrease of 24% is less than what would be anticipated. The sponsor has argued that the data is not inconsistent with other lovastatin data reported in the literature; without review of that data, the sponsor's arguments cannot be substantiated.

Table 14. Lovastatin 40 mg LDL responses

Source	LDL
LOVA Label	
1X day	-31%
1X day	-32%
AFCAPS	-26%
by baseline quartiles	
<141	-14%
141-153	-24%
154-170	-28%
>170[1]	-31%
EXCEL	
1X day	-30%
Nicostatin studies	
406 OC	-32%
414 OC	-24%

Reviewer's Comments on Study 414

Given the design and this reviewer's criteria for making a comparison, Study 414 provides no comparative data on any of the Nicostatin doses that the sponsor plans to market. This study can provide only descriptive data on the to-be-marketed Nicostatin doses. This reviewer's overall summary of the results includes a discussion of this descriptive data.

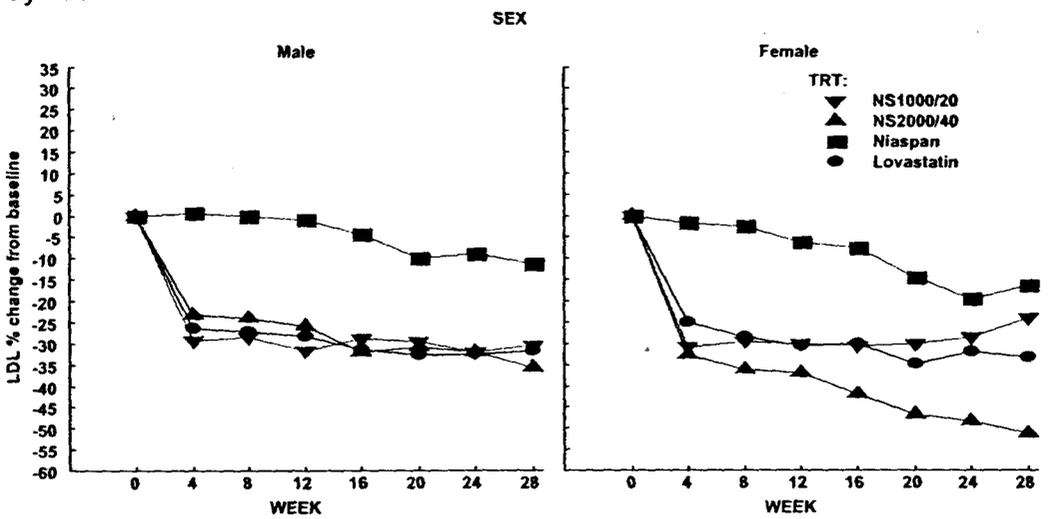
[1] Baseline for this quartile most closely matches the baseline LDL seen in Study 414.

Subgroup Analyses

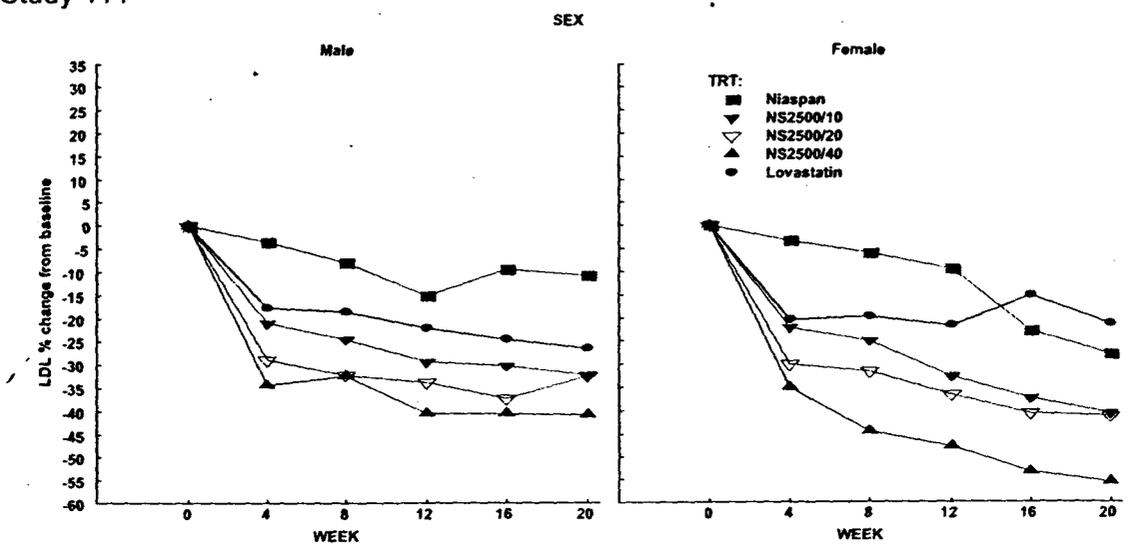
This reviewer examined the LDL results in both studies by subgroups defined by race, age (<65 versus ≥65), baseline LDL and gender. There were too few non-Caucasians to assess results by race. No differential subgroup effects were seen for age and baseline LDL. For gender, a significant interaction for gender by treatment was seen in Study 406 ($p<.02$); the interaction in Study 414 was not significant with a p-value>.2. The results by gender are shown in Figure 3 below. The results for males in Study 406, show essentially no difference between the Nicostatin arms and lovastatin arms. The difference between the genders appears to be due to the niaspan component (the label for niaspan reports a small gender difference).

Figure 3. LDL % change from baseline by gender and treatment

Study 406



Study 414



Overall Summary

The sponsor has submitted the results of two controlled Phase III studies (Studies 406 and 414) to demonstrate the efficacy of Nicostatin. The designs of these trials are summarized in Tables 3 and 9. There are several drawbacks to these designs:

1) There is a lack of independence between the dose groups. That is, the same patients within a single study are used to assess each dose of Nicostatin.
2) No comparisons in Study 406 are replicated in Study 414.
3) The titration used in Study 406 does not follow the recommended titration in the labeling.

In spite of these drawbacks this reviewer thinks the data from these trials is sufficient to assess the efficacy of Nicostatin since both components of Nicostatin are approved products with well-understood effects.

With this NDA the sponsor intended to show that Nicostatin could be marketed as first-line therapy for LDL lowering. The FDA's DMEDP has proposed that instead of first-line therapy, that Nicostatin may be used as a convenience product for those patients seeking the individual benefits of lovastatin and niaspan.

In this review, the results of analyses which address both potential indications are presented (see Reviewer's Methods on page 4 for more details). These results are summarized and discussed below. Note that presented here are only the statistical results that relate to the two indications; the clinical issues are discussed in detail by the medical reviewer and play a large role in interpretation of these results.

Indication for first-line LDL lowering

In order to show that Nicostatin may be used as first-line therapy for LDL lowering, Nicostatin must beat each component on LDL. In both studies, every dose of Nicostatin is more efficacious than niaspan at lowering LDL ($p<.0001$). The results as p-values for Nicostatin versus lovastatin are shown in Table 15 below.

Table 15. Summary of LDL Results for Nicostatin versus Lovastatin

Study	Nicostatin Dose	Lovastatin Dose	p-value
414	500/10	10	NS
414	1000/10	10	NS
406	500/20	20	NS
406	750/20	20	NS
406	1000/20	20	NS
414	**1500/20**	**20**	**.001**
414	**2000/20**	**20**	**.0001**
406	1000/40	40	NS
406	1500/40	40	NS
406	**2000/40**	**40**	**.002**
414	**2500/40**	**40**	**.0001**

Of the significant doses, only 2000/40 is a proposed marketed dose. A subgroup analysis of the 2000/40 dose showed a significant difference in treatment effects between males and females. Males showed essentially no difference between NIC 2000/40 and lovastatin 40 while the females showed a large difference (see **Figure 3**). This difference between the genders was primarily due to a difference in niaspan response. With benefit limited to females and one dose, Nicostatin does not perform well as a first-line therapy for LDL lowering.

Indication for convenience product

In order to show that Nicostatin is beneficial as a convenience product, Nicostatin must beat niaspan on LDL to show the contribution of lovastatin and Nicostatin must beat lovastatin on HDL and TG to show the contribution of niaspan. In both studies, every dose of Nicostatin is more efficacious than niaspan at lowering LDL ($p<.0001$). The results as p-values for Nicostatin versus lovastatin for HDL and TG are shown in Tables 16 and 17 below.

Table 16. Summary of HDL Results
Nicostatin versus Lovastatin: Contribution of Niaspan to Nicostatin

Study	Nicostatin Dose	Lovastatin Dose	p-value
414	500/10	10	NS
406	**500/20**	20	.005
406	**750/20**	20	.0001
414	**1000/10**	10	.0001
406	**1000/20**	20	.0001
406	**1000/40**	40	.0001
414	**1500/20**	20	.0001
406	**1500/40**	40	.0001
414	**2000/20**	20	.0001
406	**2000/40**	40	.0001
414	**2500/40**	40	.0001

Table 17. Summary of TG Results
Nicostatin versus Lovastatin: Contribution of Niaspan to Nicostatin

Study	Nicostatin Dose	Lovastatin Dose	p-value
414	500/10	10	NS
406	500/20	20	NS
406	750/20	20	NS
414	**1000/10**	10	.03
406	**1000/20**	20	.01
406	**1000/40**	40	.01
414	**1500/20**	20	.03
406	**1500/40**	40	.0006
414	**2000/20**	20	.0001
406	**2000/40**	40	.0002
414	**2500/40**	40	.0001

Among the doses proposed for marketing, the doses showing sufficient efficacy for approval as a convenience product are Nicostatin 1000/20, 1000/40, 1500/40 and 2000/40.

Size of treatment effects

Comparative data on the four doses of Nicostatin shown to offer benefit is available from Study 406 only and shown in Table 18 below. This reviewer would recommend the use of this table in the **labeling** because it reflects the design of Study 406 and clearly shows changes over time in each group for all three lipid measures.

Table 18. Study 406 lipid percent change from baseline (LOCF mean)

Week	Nicostatin (n=52)		Niaspan (n=55)		Lovastatin (n=59)	
	Dose	LDL	Dose	LDL	Dose	LDL
12	1000/20	-30%	1000	-3%	20	-29%
16	1000/40	-35%	1000	-5%	40	-31%
20	1500/40	-36%	1500	-10%	40	-33%
28	2000/40	-40%	2000	-10%	40	-31%
	Dose	HDL	Dose	HDL	Dose	HDL
12	1000/20	+19%	1000	+12%	20	+3%
16	1000/40	+19%	1000	+12%	40	+5%
20	1500/40	+26%	1500	+18%	40	+5%
28	2000/40	+28%	2000	+19%	40	+6%
	Dose	TG	Dose	TG	Dose	TG
12	1000/20	-26%	1000	-13%	20	-15%
16	1000/40	-32%	1000	-18%	40	-15%
20	1500/40	-37%	1500	-22%	40	-18%
28	2000/40	-40%	2000	-20%	40	-20%

Study 414 did not provide comparative data for the Nicostatin doses proposed for marketing but does provide descriptive data. This reviewer examined the 406 responses above against the responses seen in Study 414. Boxplots for all three outcome parameters and for each of the four doses are presented in Appendix 3. (Note, for the 1000/20 dose, the results in the table above are for the 2000/40 arm at Week 12 while in the boxplot, the results for the 1000/20 arm at Week 28 are used. Examination of the curves in Appendix 1 show essentially no change in response after Week 12 for the 1000/20 arm and nearly identical responses to the 2000/40 arm up to Week 12.)

When looking at the boxplots, remember that the data for doses 1000/40, 1500/40 and 2000/40 come from the same set of patients in each of the studies. Therefore, it is not surprising that the relationship seen between the studies is the same for all three lipid parameters; namely, 1) overlapping responses for LDL and HDL and 2) a larger triglyceride response in Study 406 then 414. These observations also hold for dose 1000/20.

The sponsor proposes [redacted] in the label. This reviewer is opposed to [redacted] primarily due to the differences between the trial designs. Also, comparative data is only available in Study 406 and it is the data that will provide the basis for approval.

Overall Conclusions

Based on the statistical data from Studies 406 and 414, this reviewer concludes the following:

1. Nicostatin (doses≥1000/20) is efficacious at lowering LDL compared to niaspan and raising HDL and lowering TG compared to lovastatin suggesting that Nicostatin may be useful as a convenience product.
2. The data is insufficient to support Nicostatin as first line therapy for LDL lowering for the following reasons:
   - Only one dose of Nicostatin (2000/40) beats lovastatin alone for LDL lowering
   - The effect of the 2000/40 dose is only seen in females, not in males
   - Comparative data on 2000/40 is only available from one trial
3. Data from doses below 1000/20 are useful for titration only;
4. Only the efficacy data from Study 406 should be included in the label because it is representative of other data submitted in this NDA and provides the primary basis for approval.
5. Nicostatin is not tolerated by about one-third of patients. In the two clinical trials, about 2.5 times as many patients randomized to Nicostatin discontinured treatment compared to lovastatin.

Specific comments on The Clinical Trials section of the label are not presented here because the section is unacceptable generally and will require several meetings of the review team to reformulate.

Joy D. Mele, M.S.
Mathematical Statistician

Concur:

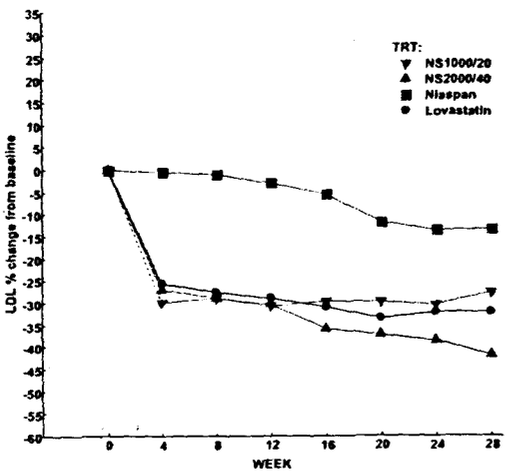
Todd Sahlroot, Ph.D.
Team Leader

APPEARS THIS WAY
ON ORIGINAL

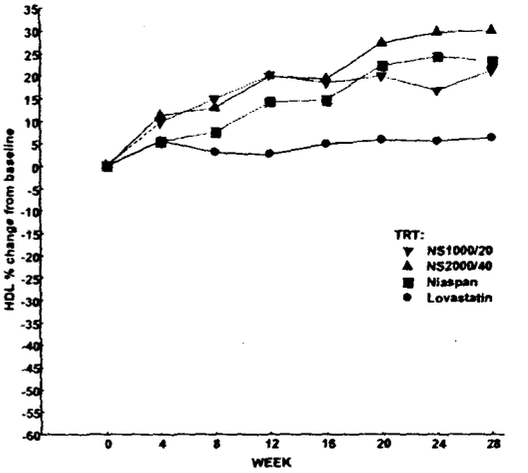
Ed Nevius, Ph.D.
Director of DOB2
cc:
Archival NDA#21-249
HFD-510
HFD-510/MParks, APariser,Wkoch, DOrloff
HFD-715/ JMele, TSahlroot, ENevius, CAnello
Mele/x76376/DOB2/Word-nicostat.rev2.doc/April 3, 2001

Appendix 1. % change from baseline for lipid parameters for observed cases in Study 406

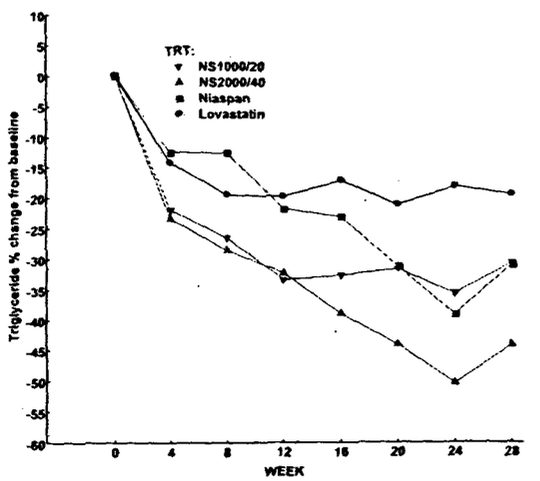
LDL % change from baseline



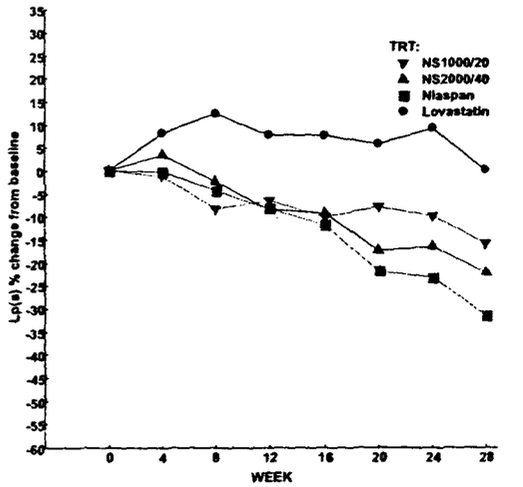
HDL % change from baseline



TG % change from baseline (medians)



Lp(a) % change from baseline

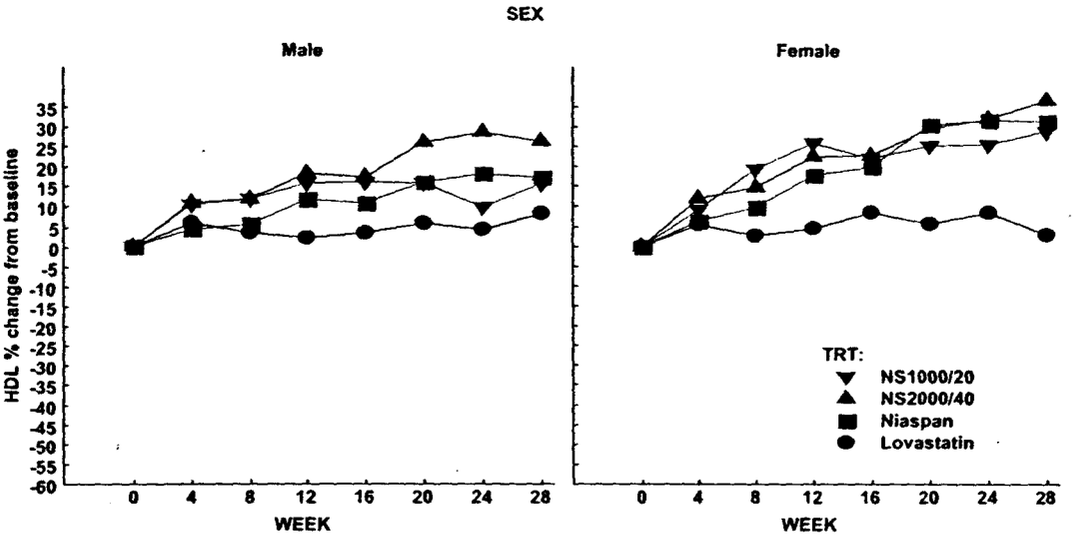


Dose by week on study

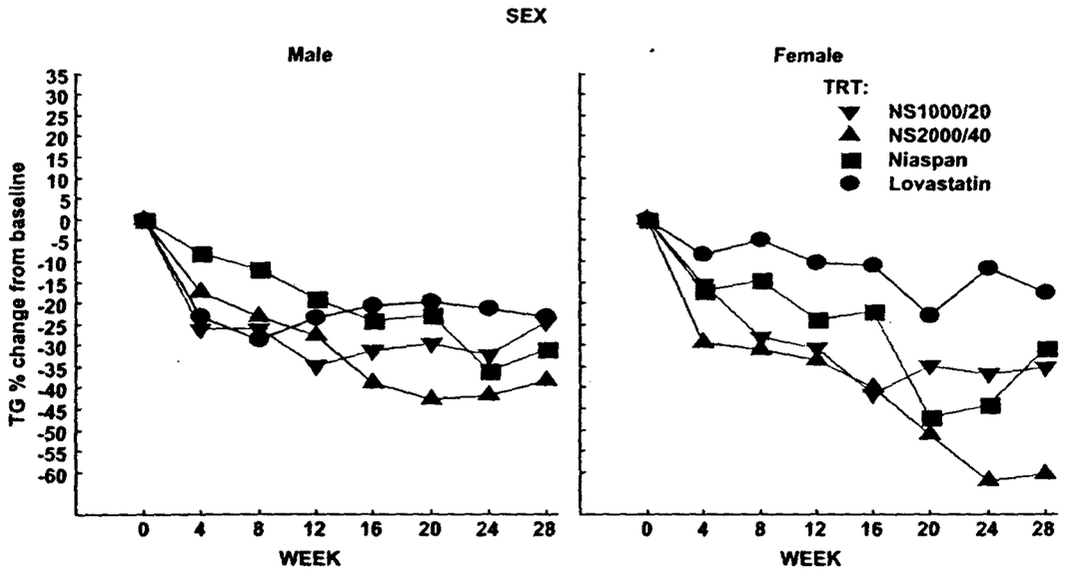
Treatment Group	WEEK						
	1-4	4-8	8-12	12-16	16-20	20-24	24-28
NS 1000/20 ▼	500/20	750/20	1000/20	1000/20	1000/20	1000/20	1000/20
NS 2000/40 ▲	500/20	750/20	1000/20	1000/40	1500/40	2000/40	2000/40
NIA 2000 ■	500	750	1000	1000	1500	2000	2000
LOVA 40 ●	20	20	20	40	40	40	40

Appendix 2. % change from baseline for HDL and TG by gender for observed cases in Study 406

HDL (means)



TG (medians)



Dose by week on study

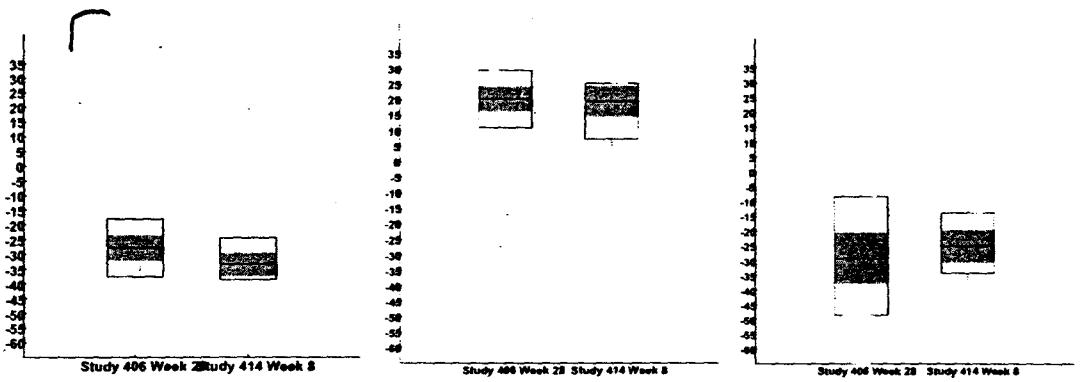
Treatment Group	WEEK						
	1-4	4-8	8-12	12-16	16-20	20-24	24-28
NS 1000/20 ▼	500/20	750/20	1000/20	1000/20	1000/20	1000/20	1000/20
NS 2000/40 ▲	500/20	750/20	1000/20	1000/40	1500/40	2000/40	2000/40
NIA 2000 ■	500	750	1000	1000	1500	2000	2000
LOVA 40 ●	20	20	20	40	40	40	40

Appendix 3. Comparison of study results for four Nicostatin doses

Boxplots of % change from baseline for LDL, HDL and TG (LOCF) for Studies 406 (first box) and 414 (second box)

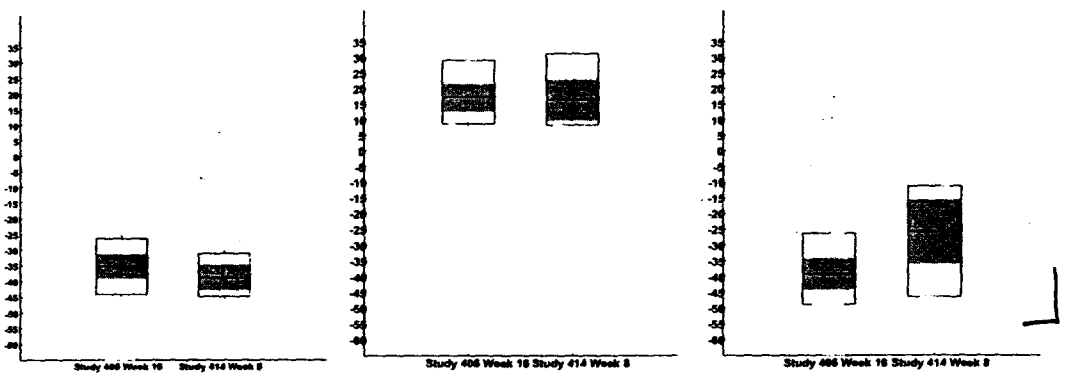
Nicostatin 1000/20 (Study 406 Week 28 and Study 414 Week 8)

LDL **HDL** **TG**



Nicostatin 1000/40 (Study 406 Week 16 and Study 414 Week 8)

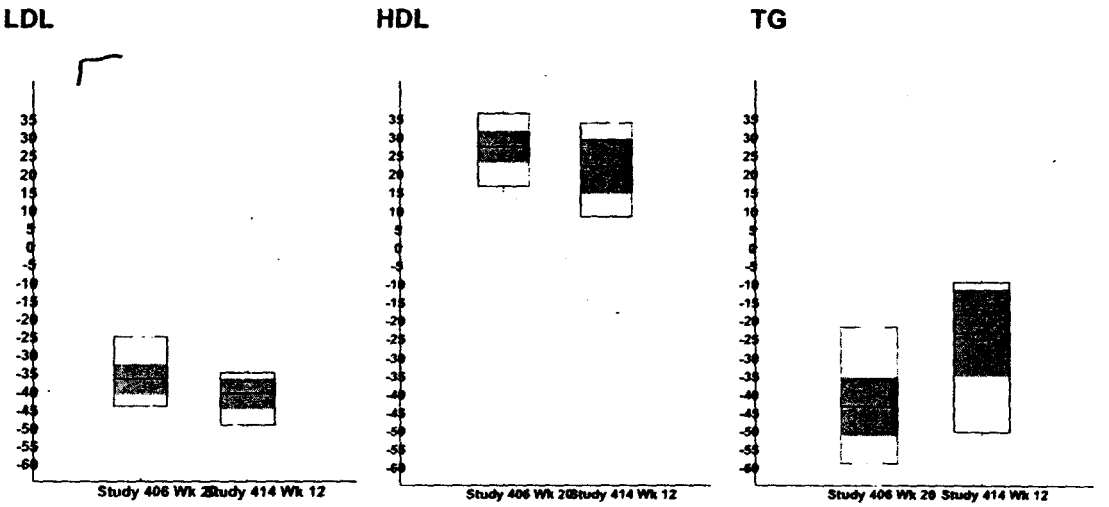
LDL **HDL** **TG**



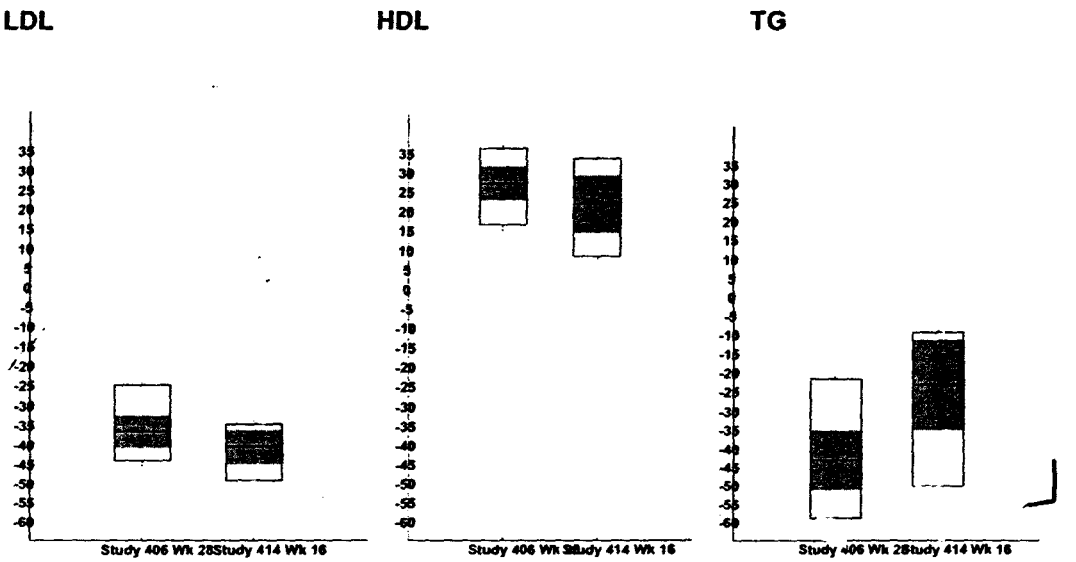
Appendix 3. Comparison of study results for four Nicostatin doses (cont.)

Boxplots of % change from baseline for LDL, HDL and TG (LOCF) for Studies 406 (first box) and 414 (second box)

Nicostatin 1500/40 (Study 406 Week 20 and Study 414 Week 12)



Nicostatin 2000/40 (Study 406 Week 28 and Study 414 Week 16)



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Joy Mele
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BIOMETRICS

S. Edward Nevius
5/2/01 03:09:10 PM
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Concur with review.

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