# Efficacy and Safety of An Extended-Release Niacin (Niaspan): A Long-Term Study

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**Crystalline nicotinic acid (immediate-release niacin) is effective therapy for lipoprotein regulation and cardiovascular risk reduction. However, inconvenient regimens and unpleasant side effects decrease compliance. Sustained-release formulations designed to circumvent these difficulties increase hepatotoxicity. Niaspan, a new US Food and Drug Administration (FDA)-approved, once-daily, extended-release form, has been found effective and safe in short-term trials. The long-term efficacy and safety of Niaspan lipid monotherapy was studied in 517 patients (aged 21–75 years) for ≤96 weeks in dosages ≤3,000 mg/day. Primary efficacy endpoints were low-density lipoprotein (LDL) cholesterol and apolipoprotein B (apo B) changes from baseline; secondary efficacy endpoints were changes in total cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, lipoprotein(a), and total cholesterol/HDL-cholesterol ratio; safety data included adverse events and laboratory values over the 2-year study period. LDL-cholesterol levels decreased significantly: 18% at week 48 and 20% at week 96; apo B reduction was similar (16% decrease at week 48 and 19% at week 96). Large elevations in HDL cholesterol (26%, week 48; 28%, week 96) allowed only modest decreases in total cholesterol (12% and 13%, respectively), whereas total cholesterol/HDL-cholesterol ratio decreased by almost one third. Triglyceride and lipoprotein(a) levels were decreased by 27% and 30%, respectively (week 48), and by 28% and 40%, respectively (week 96). All changes from baseline were significant ($p < 0.001$). Niaspan was generally well tolerated, although flushing was common (75%); however, there was a progressive decrease in flushing with time from 3.3 episodes in the first month to ≤1 episode by week 48. Aspirin was used by one third of patients before Niaspan dosing to minimize flushing episodes. Although serious adverse events occurred in about 10% of patients, none were considered probably or definitely related to Niaspan. Adverse events in general varied widely, but their true relation to the study drug is difficult to ascertain without a placebo (control) group. No deaths occurred. There were statistically significant changes in hepatic transaminases, alkaline phosphatase, direct bilirubin, phosphorus, glucose, amylase, and uric acid. However, these changes were mostly small and are not likely to be biologically or clinically significant (the decrease in phosphorus is a new finding in niacin therapy). No myopathy was observed. Thus, this long-term study confirms the earlier short-term findings that Niaspan is safe and effective as monotherapy in plasma lipoprotein regulation.** 

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For >40 years, pharmacologic doses of crystalline nicotinic acid (immediate-release niacin) have been utilized effectively for the therapy of various lipoprotein abnormalities.[1–3] Immediate-release niacin is unique thus far among plasma lipid-regulating agents in that it effectively changes all major lipoprotein analytes in a favorable direction. Its favorable effects on low-density lipoprotein (LDL) cholesterol, triglycerides, high-density lipoprotein (HDL) cholesterol, $HDL_2$ cholesterol, lipoprotein(a), apolipoprotein B (apo B), and apolipoprotein A-I (apo A-I) are substantial. Immediate-release niacin has thus been indicated as first-line therapy for management of elevations of LDL cholesterol and/or triglycerides.[4] Immediate-release niacin was the first monotherapy shown to produce significant lowering of cardiovascular endpoints, and cardiovascular and all-cause mortality.[5,6]

Nevertheless, despite their effectiveness in lipoprotein regulation and benefit in cardiovascular risk reduction, preparations of immediate-release niacin have been underutilized in lipid-lowering regimens, largely because of compliance problems stemming from nuisance side effects, the need for multiple daily dosing with food, and inadequate implementation of gradual dose titration. Flushing, a pharmacologic effect of the drug, and other bothersome cutaneous reactions, have constrained its use by patients and physicians for therapy of lipid abnormalities.

Controlled-release (sustained-release) preparations of niacin were developed to circumvent these problems and thereby improve long-term compliance. However, such preparations have raised concerns because of their unfavorable safety profiles, particularly with respect to hepatotoxicity. Moreover, these preparations also cause flushing episodes that are often delayed but longer lasting. In addition, gastrointestinal side effects and adverse metabolic consequences of

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these formulations have generally rendered them unsafe, particularly for long-term use.

Niaspan, an extended-release preparation of niacin, is the first formulation of its kind approved by the US Food and Drug Administration (FDA) for efficacy and safety. This drug is indicated for the long-term treatment of hypercholesterolemia and/or hypertriglyceridemia.

The following report describes the efficacy and safety of Niaspan administered as monotherapy to 517 patients for periods of up to 96 weeks in dosages of up to 3,000 mg/day.

## METHODS AND STUDY PLAN

**Objectives:** The primary goal of this open-label study was to assess the long-term safety and efficacy of Niaspan taken once nightly by patients with primary hypercholesterolemia. Primary efficacy endpoints were percent changes from baseline in LDL cholesterol and apo B. Secondary efficacy endpoints included percent changes from baseline in the following parameters: total cholesterol, triglycerides, HDL cholesterol, lipoprotein(a), and total cholesterol/HDL-cholesterol ratio. Safety data included adverse events and laboratory data from patients over a 2-year period.

**Study design:** Patients with primary hypercholesterolemia who had been enrolled in previous randomized, shorter-term studies or in a placebo-only qualification clinical trial were recruited (27 study sites). All patients entering this open-label extension trial were given a 4-week titration pack of Niaspan for upward retitration. Dosing was initiated at 375 mg nightly with food for 1 week at bedtime after a low-fat snack, then 500 mg nightly was taken for 1 week, and finally, 1,000 mg (2 × 500 mg) was taken for 1 week at bedtime after a low-fat snack (Table I). Aspirin 325 mg taken 30 minutes before dosing could be utilized for prophylaxis and treatment of flushing. After initial titration, Niaspan dosages prescribed were 1,000–3,000 mg once nightly, depending on the investigator's clinical judgment of the patient's therapeutic response and evaluation of adverse experiences. Treatment visits were distributed over about 24 months. Visits 15 and 17 (48 and 96 weeks) were considered the 1- and 2-year time periods. The protocol was approved by the Institutional Review Boards of the 27 participating study sites, and written informed consent was obtained from all patients enrolled.

Primary entry criteria were as follows: men and women aged 21–75 years with (1) baseline LDL-cholesterol levels of 160–190 mg/dL, with either stable coronary artery disease or without overt coronary artery disease but with at least 2 coronary artery disease risk factors; or (2) with baseline LDL-cholesterol levels >190 mg/dL, without detectable coronary artery disease or coronary artery disease risk factors. Other baseline lipoprotein requirements included serum triglycerides <800 mg/dL (9 mmol/L) and HDL cholesterol ≤70 mg/dL (1.81 mmol/L). Patients with secondary hyperlipidemia were excluded. Also excluded were patients with a clinically significant history of diabetes mellitus, gout, peptic ulcer disease, cardiac arrhythmias, or any major or currently active illness that might affect plasma lipid levels. Premenopausal women were enrolled into the trial, provided they were surgically sterile or using oral contraceptives. Suitable patients with stable medical conditions, such as primary hypertension, treated with medication unlikely to alter plasma lipid levels and patients taking a stable, adequate dose of thyroxine replacement therapy were eligible for enrollment.

**TABLE I** Niaspan Dosing and Visit Schedule

| Week(s) of Dosing | Niaspan Daily Bedtime Dose (mg) | Visit Number When Drug Was Dispensed |
|---|---|---|
| 1–4* | 375<br>500<br>750<br>1,000 | 11 |
| 4† | 1,000–3,000‖ | 12 |
| 12‡ | | 13 |
| 24‡ | | 14 |
| 48§ | | 15 |
| 72§ | | 16 |
| 96§ | | 17 |
| 98 | Same as visit 17 | Visit 17 follow-up |

*Initial titration.
†±3 days.
‡±7 days.
§Six months from last visit ±7 days.
‖Per investigator's discretion.

Dietary diaries were reviewed with patients at each visit to promote compliance with the American Heart Association Step One Diet.

Niaspan plus concomitant therapy with a statin, a bile acid sequestrant, or both was permitted for patients who did not, in the investigators' judgment, achieve sufficient LDL-cholesterol reduction while taking either a maximally tolerated dose or 2,000 mg/day of Niaspan. Decisions regarding the maximally tolerated dose of the drug or the addition of concomitant drug were left to the discretion of the clinical investigators. This report is largely confined to the data obtained from those patients maintained on long-term therapy with Niaspan as the sole lipid-regulating medication.

**Study measurements:** Twelve-hour fasting blood samples were collected at each patient visit (Table I). Laboratory analyses of study specimens for efficacy and safety parameters were carried out either at the University Hospital Clinical Chemistry Laboratory (Cincinnati, Ohio) or Northwest Lipid Research Laboratory (Seattle, Washington). Both laboratories are certified by the Centers for Disease Control and Prevention–the National Heart, Lung, and Blood Institute Lipid Standardization Program. Serum concentrations of total cholesterol and subfraction lipoprotein cholesterol were measured spectrophotometrically after sample pretreatment with the cholesterol oxidase method. HDL cholesterol, HDL cholesterol subfractions, triglyceride, apolipoproteins, and lipoprotein(a) levels were measured as previously described.[7] LDL cholesterol was calculated according to the Friedewald equation when serum triglycerides were <400 mg/dL or by

**TABLE II** Baseline Lipid, Lipoprotein, and Apolipoprotein Levels in Patients Treated with Niaspan Monotherapy

| Analyte | Baseline Levels (mg/dL) (n = 517) |
|---|---|
| LDL cholesterol | 195 ± 1.5 |
| Apolipoprotein B* | 149 ± 1.5 |
| HDL cholesterol | 45 ± 0.4 |
| Total cholesterol | 275 ± 1.6 |
| Triglycerides | 174 ± 13.4 |
| Lipoprotein(a)* | 38 ± 2.4 |
| Total/HDL cholesterol | 6.3 ± 0.1 |

Data presented as mean ± SEM.
HDL = high-density lipoprotein; LDL = low-density lipoprotein.
*Apolipoprotein B and lipoprotein(a) were analyzed in a subset of 275 patients treated with Niaspan only. The above baseline levels were those that were applicable to patients who received Niaspan monotherapy.

beta quantification after ultracentrifugal flotation when serum triglycerides were >400 mg/dL.

**Data analyses:** Baseline levels were established as the average of 2 or 3 consecutive determinations made 1 week apart just before randomization in the shorter-term trials or during the qualifying trial. Matched-pair *t* tests were used in the within-group analyses to assess mean percentage change from baseline for each efficacy variable. In addition, the primary (LDL cholesterol and apo B) and selected secondary (total cholesterol, HDL cholesterol, lipoprotein(a), apo A-I, total cholesterol/HDL-cholesterol ratio, LDL-cholesterol/HDL-cholesterol ratio, and triglycerides) efficacy endpoints were analyzed at baseline, week 48, and week 96 in patients who received Niaspan only. Safety laboratory parameters were summarized and statistically analyzed with significance established at $p \leq 0.05$. Adverse events (excluding flushing) were coded by COSTART terminology and summarized for the intent-to-treat group and subgroups at week 48 and week 96. Adverse events were compared by the number of patients reporting an event, the frequency of individual events, and for body systems. The number of patients experiencing flushing events, the number of flushing events per patient, and the intensity and duration of these events were recorded and summarized.

**Patients:** The primary analysis included 723 patients who were enrolled in the open-label extension study, the vast majority of whom participated in the previous randomized trials with Niaspan. The mean age at entry was 54 years, and the gender distribution among men and women was, respectively, 70% and 30%. More than 90% of participants were non-Hispanic whites. Of this intent-to-treat population, 517 patients received Niaspan alone (i.e., without concomitant lipid-lowering medications) for periods of up to 2 years. By week 48 (1 year), 320 patients remained in the trial, and by week 96, 225 patients continued on Niaspan only. Compliance with taking the drug (by pill counts) was ≥95%. Of those patients who discontinued, 28% dropped out for medical reasons unrelated to Niaspan or for adverse events considered by the investigator to be only remotely related to study medications. Dropouts for nonmedical reasons such as lack of cooperation, inconvenience, relocation, or patient or referring physician preference amounted to 25%. The median dosage of Niaspan taken by study participants was 2,000 mg daily, and the mean duration of Niaspan monotherapy was 59.4 weeks. Of the intent-to-treat population, about 70% were treated with Niaspan monotherapy and the remainder with Niaspan in combination with a statin and/or bile acid sequestrant, according to the clinical judgment of individual investigators.

## RESULTS

**Efficacy:** Mean baseline levels of LDL cholesterol and apo B of those who did not receive concomitant lipid-lowering medications were, respectively, 195 and 149 mg/dL (Table II). LDL-cholesterol levels decreased significantly with Niaspan therapy: 18% at week 48 and 20% at week 96. Apo B reductions were of similar magnitude (16% decrease by week 48 and 19% by week 96). In addition, Niaspan therapy produced striking elevations in mean HDL-cholesterol levels of 26% and 28%, respectively, at weeks 48 and 96 (Figure 1 and Table III). Because of these HDL-cholesterol elevations, the decreases in total cholesterol were only modest at 12% and 13%, and the total cholesterol/HDL-cholesterol ratio decreased by nearly one third (Figure 2 and Table III). After 48 weeks of Niaspan monotherapy, plasma triglyceride and lipoprotein(a) levels were decreased by 27% and 30%, respectively; levels were decreased by 28% and 40%, respectively, after 96 weeks of therapy (Figure 2 and Table III). No tendency for this efficacy to wane was observed over the 96-week span of the study. For both the primary and the selected secondary endpoints of efficacy, the percent changes achieved by both 48 and 96 weeks of therapy were statistically significant ($p < 0.001$).

**Safety:**

SIDE EFFECTS AND ADVERSE EVENTS. The side effects in the long-term studies of Niaspan were similar to those observed in the shorter-term trials. The drug was generally well tolerated. Flushing is a common occurrence in patients taking all forms of niacin. As shown in Figure 3, about 75% of patients experienced treatment-related flushing over the 96 weeks of the trial, a pharmacologic effect of the drug. Also, the great majority of patients who continued Niaspan therapy developed tolerance to the flushing, and a progressive decrease in flushing occurred with prolonged use. In those patients who reported flushing, there were 3.3 flushing episodes per patient in the first month, but the number of episodes per month decreased sharply with time to ≤1 episode per month (Figure 3). If all patients in the study population were considered as the base, the frequency of flushing episodes was even smaller. About one third of the patients utilized aspirin beforehand to minimize flushing episodes.

SERIOUS AND UNEXPECTED ADVERSE EVENTS. Serious and unexpected adverse events, including those that were life-threatening or required hospitalization, occurred in 75 of the 723 patients. Twenty-three events

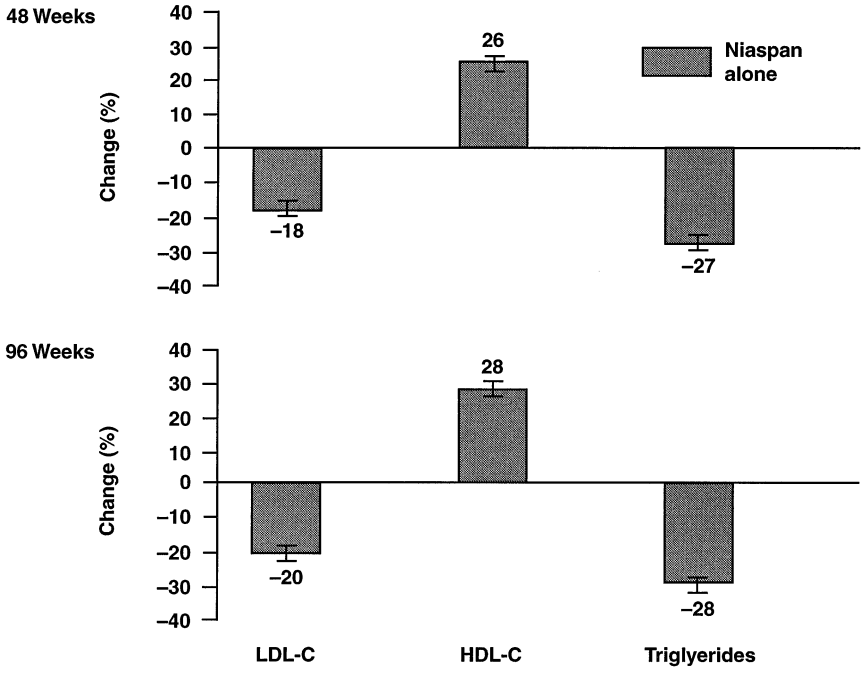


**FIGURE 1. Changes (%) from baseline in low-density lipoprotein cholesterol (LDL-C), high-density lipoprotein cholesterol (HDL-C), and triglyceride levels. All changes from baseline are significant, p <0.001.**

were hospitalizations related to cardiovascular causes; the remainder were necessitated by a wide range of indications, including trauma, elective surgery, gastrointestinal, renal, infectious, musculoskeletal, neoplastic, and nonspecific causes. Of these events, 64 were considered not related to Niaspan, 8 were considered remotely related, and 3 possibly related. No deaths occurred.

Table IV enumerates a range of adverse experiences and their frequency. The kinds of events listed varied widely and were considered at least remotely related to the study drug in ≥5% of patients. These included gastrointestinal, cutaneous, pruritic, or painful, but their true relation to the study drug is difficult to ascertain without a placebo patient group. Moreover, this kind of side-effect listing has been commonly recorded with a variety of therapeutic agents.

**TABLE III** Mean Lipid, Lipoprotein, and Apolipoprotein Changes From Baseline: Results at 48 and 96 Weeks

| | Change from Baseline (%) | |
|---|---|---|
| Analyte (mg/dL) | Week 48 (n = 320) | Week 96 (n = 225) |
| LDL cholesterol | −18* (0.7) | −20 (0.9) |
| Apolipoprotein B† | −16* (1.3) | −17* (1.7) |
| HDL cholesterol | 26* (1.1) | 28* (1.3) |
| Total cholesterol | −12* (0.6) | −13 (0.7) |
| Triglycerides | −27* (1.7) | −28 (2.0) |
| Lipoprotein(a)† | −30* (6.9) | −39 (3.0) |
| Total/HDL cholesterol | −29* (0.8) | −31* (0.9) |

Numbers in parentheses represent ± standard error.
*p <0.001 by matched-pair *t* test comparing differences from baseline.
†The changes in apolipoprotein B and lipoprotein(a) were based on analyses obtained from a subset of patients (n = 91, week 48; n = 73, week 96).

LABORATORY MONITORING. Among the clinical chemistry parameters itemized in Table V, there were statistically significant changes in hepatic transaminases, alkaline phosphatase, direct bilirubin, phosphorus, glucose, amylase, and uric acid levels. However, for the most part, the changes observed were small and not likely to be biologically or clinically significant. The decrease in serum phosphorus is a new finding in niacin therapy; about one fourth of the patients experienced a decrease below the lower limit of normal (<2.5 mg/dL) at some time. A few patients experienced serum fasting glucose levels <130 mg/dL and serum amylase elevations about twice the upper limit of normal. Hepatic transaminases, particularly aspartate aminotransferase, rose significantly but remained within the normal range. Only 6 patients (<1%) had aspartate aminotransferase elevations >2 times the upper limit of normal, and 2 patients (<1%) had aspartate aminotransferase increases >3 times the upper limit on Niaspan monotherapy. Five patients (<1%) had alanine aminotransferase (ALT) elevations >2 times the upper limit, and none had ALT increases >3 times the upper limit. Since all these changes in biochemical parameters were tracked over 96 weeks of therapy, and were present to varying degrees over the course of therapy, they do not, for the

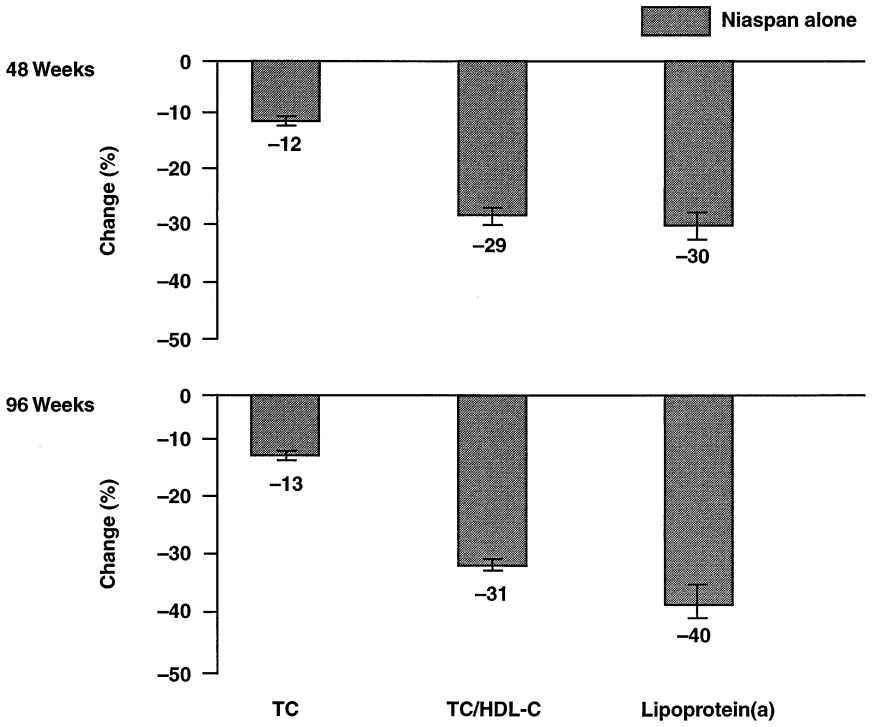


**FIGURE 2. Changes (%) from baseline in total cholesterol (TC), TC/high-density lipoprotein cholesterol (HDL-C), and lipoprotein(a). All changes from baseline are significant, p <0.001.**

most part, appear to pose safety issues. No cases of myopathy were observed at any time during the trial.

As shown in Table VI, mean platelet counts decreased by 10.1% at week 48 and 14.8% at week 96, whereas leukocyte counts increased by 6.5% and 6.8%, respectively, at week 48 and week 96 of therapy. Although these changes are small, they are consistent and statistically significant ($p < 0.0001$). However, their biologic and clinical significance at this time is unclear. All other hematologic parameters that were followed on Niaspan monotherapy appeared variable and unremarkable.

## DISCUSSION

Crystalline niacin has had a long and successful history as an effective antihyperlipidemic drug since

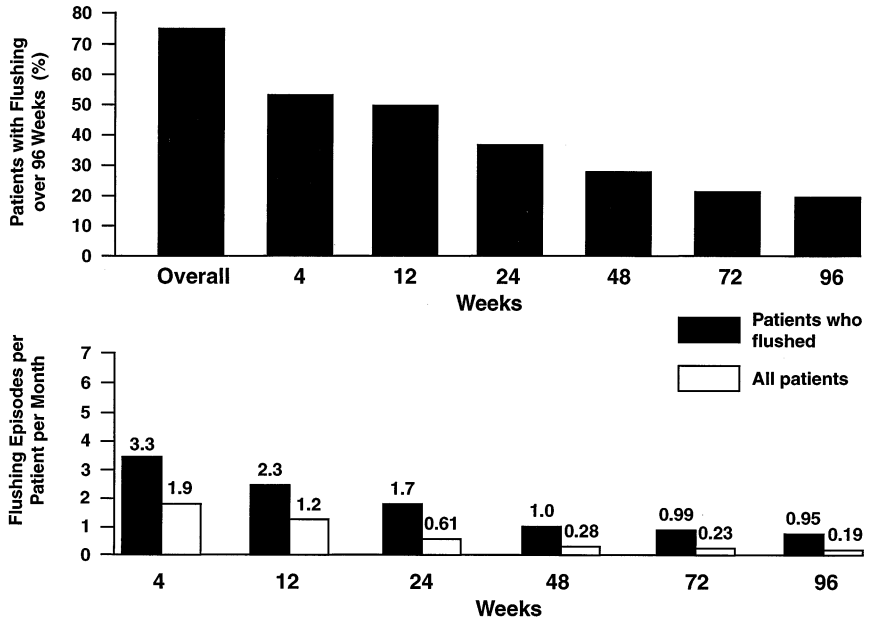


**FIGURE 3. Occurrence and frequency of flushing during the study.**

1955. Although used successfully in combination therapy with other serum lipid-regulating agents in several cardiovascular endpoint trials,[8–10] niacin monotherapy itself decreased both nonfatal myocardial infarction incidents[5] and all-cause mortality[6] in male survivors of a previous coronary event. An earlier long-term study of niacin for hypercholesterolemia demonstrated favorable efficacy for cholesterol lowering with gastrointestinal symptoms as the major side effects.[2] However, use of crystalline niacin is often problematic because of its inconvenience, need for multiple daily dosing, bothersome side effects, and problems encountered with over-the-counter brands that have not undergone vigorous product and clinical testing and regulatory review for safety and efficacy. Thus, the lower costs of nonprescription brands of crystalline niacin do not outweigh the drawbacks of lack of consistency in bioequivalence and in product quality.

Niaspan is the first extended-release preparation of niacin approved by the FDA as a safe and effective drug for the management of lipid disorders. In general other sustained-release preparations of niacin have raised various safety issues, especially with regard to a greater frequency and severity of gastrointestinal effects, particularly hepatotoxicity. Small comparative studies[11,12] and case reports[13,14] have provided evidence that other sustained-release niacin formulations have greater potential for hepatic dysfunction and severe hepatotoxicity than comparable doses of immediate-release niacin. Of particular concern is the lack of long-term safety and efficacy data with any existing sustained-release niacin formulation. By contrast, Niaspan, an extended- or controlled-release formulation of niacin, is the only such preparation that has met the safety and efficacy standards of the FDA with labeling both for lipid-lowering and for cardiovascular risk reduction. A prior report of its therapeutic effects had already demonstrated its favorable short-term safety and efficacy,[7] and other long-term data reported on Niaspan[15] confirmed continuation of these treatment benefits over time.

The present study summarizes the overall long-term beneficial effects of Niaspan as monotherapy for plasma lipoprotein regulation, with substantial sustained effects on LDL cholesterol, apo B, triglycerides, HDL cholesterol, lipoprotein(a), and other secondary endpoints that were comparable to those observed in shorter-term, well-controlled studies.[7,15] Since there was considerable flexibility given to investigators to use clinical judgment in dosage adjustments and the use of concomitant lipid-lowering drugs, the data obtained are likely quite similar to conditions that hold for the community-living hyperlipidemic population. Indeed, the elevated mean baseline levels of LDL cholesterol in the various lipid center study sites are considerably higher than are usually encountered in most outpatient practice populations, and therefore substantial nightly doses of Niaspan (median doses of 2,000 mg) were utilized. Such doses taken with a bedtime snack were found to be effective, generally well tolerated, and safe over prolonged periods of use.

In the earlier report,[7] Niaspan dosages of 2,000 mg/day for 12 weeks after a lead-in and dose-titration period produced salutary changes in serum lipoprotein levels. Significant decreases in serum total cholesterol (−10%), LDL cholesterol (−14%), triglycerides (−29%), apo B (−15.7%), and lipoprotein(a)

**TABLE IV** Most Commonly Reported Adverse Events*

| Event | All Patients (%) (n = 723) | Niaspan Monotherapy (%) (n = 517) |
|---|---|---|
| Headache | 100 (14) | 92 (13) |
| Pain† | 55 (8) | 46 (6) |
| Abdominal pain | 66 (9) | 54 (8) |
| Diarrhea | 106 (15) | 97 (13) |
| Dyspepsia | 56 (8) | 46 (6) |
| Nausea | 82 (11) | 72 (10) |
| Vomiting | 43 (6) | 38 (5) |
| Rhinitis | 41 (6) | 30 (4) |
| Pruritus | 67 (9) | 56 (8) |
| Rash | 57 (8) | 51 (7) |

*Events at least remotely related to study drug occurring in ≥5% of patients.
†Includes pain experienced in any part of the body except the abdomen.

**TABLE V** Changes in Selected Biochemical Parameters

| Parameter | Baseline Value | Endpoint* Value | Change (%) |
|---|---|---|---|
| AST (mIU/mL) | 18.7 | 22.4 | +26** |
| ALT (mIU/mL) | 23.7 | 23.9 | + 7** |
| Alkaline phosphatase (mIU/mL) | 66.0 | 66.8 | + 2** |
| Direct bilirubin (mg/dL) | 0.12 | 0.13 | + 9** |
| Phosphorus (mg/dL) | 3.49 | 3.2 | − 9** |
| Glucose (mg/dL) | 95.3 | 99.4 | + 4** |
| Amylase (mg/dL) | 50.5 | 53.1 | + 8** |
| Uric acid (mIU/mL) | 5.8 | 6.3 | +11** |

ALT = alanine aminotransferase; AST = aspartate aminotransferase.
*Endpoint values are those obtained at the last patient visit beyond 96 weeks. All changes from baseline are significant; *p <0.05; **p <0.001.

**TABLE VI** Hematologic Parameters* in Long-Term Study Patients on Niaspan Monotherapy: Weeks 48 and 96

| Parameter | Baseline Mean (n = 629) | Change (%) at Week 48 (n = 310) | Change (%) at Week 96 (n = 220) |
|---|---|---|---|
| Hemoglobin (g/dL) | 14.6 | 0.88† | −0.1 |
| Hematocrit (%) | 43.4 | 0.7 | 0.7 |
| Platelets ($10^3$/mm$^3$) | 262 | −10.1‡ | −14.8‡ |
| WBC ($10^3$/mm$^3$) | 5.7 | 6.5‡ | 6.8‡ |
| PT (s) | 11.6 | 2.3‡ | 0.0 |
| PTT (s) | 28.9 | −0.2 | −0.5 |
| RBC ($10^3$/mm$^3$) | 4.8 | 0.0 | −1.3‡ |

PT = prothrombin time; PTT = partial thromboplastin time; RBC = red blood cells; WBC = white blood cells.
*Standard hematologic parameters were measured at baseline and then sequentially over the 2-year period of the study. The matched-pair *t* test comparing differences at 48 and 96 weeks from baseline was used to determine statistical significance.
†p <0.01.
‡p <0.001.

(−27%), with a substantial increase in HDL cholesterol (23%) were observed, with minimal changes in the placebo group. Additional improvements in these efficacy parameters were observed at 48 and 96 weeks of dosing. This further long-term benefit may be attributable to improved compliance, increasing tolerance to Niaspan, a progressive metabolic response, a greater retention of better responders to the drug, or a combination of the above. However, interpretation of these long-term data must be considered carefully, with the understanding that there is no placebo group for longitudinal comparison of data in open-label studies. The same considerations apply to the interpretation of safety parameters, since patients taking a placebo will often show the same kinds of side effects.

Elevated lipoprotein(a), high triglycerides, and low HDL cholesterol in various combinations are very prevalent among patients with coronary artery disease, irrespective of their initial LDL-cholesterol levels.[16] Since this constellation of various combinations of abnormal lipoprotein analyte levels is very common among patients with premature coronary artery disease, Niaspan, which affects each of these analytes in the desired direction, should have great utility in such patients and in others at high cardiovascular risk. Of particular importance is the fact that niacin preparations are by far the most effective lipid-regulating agents for increasing HDL cholesterol[17,18] and for lowering lipoprotein(a)[3,17] levels; the long-term data with Niaspan demonstrate that its efficacy in improving these parameters continued unabated, with a substantial decrease in lipoprotein(a) levels of 30–40%. Since Niaspan was well tolerated in this study, with only 6% of study subjects discontinuing therapy due to flushing and a comparable number discontinuing because of gastrointestinal side effects that were potentially drug-related, Niaspan taken once nightly with a bedtime snack should provide an excellent therapeutic modality alone or in combination with other lipid-regulating medications. Another report of the therapeutic profile of Niaspan taken long-term in combination with a statin and/or bile-acid sequestrant demonstrated the safety and augmented efficacy in LDL-cholesterol reduction.[19] The observed compatibility of Niaspan with other agents for dyslipidemia management strongly suggests that Niaspan will have broad utility in the various populations of patients who have or who are at increased risk for, cardiovascular disease. Combination regimens that include niacin have shown the greatest degrees of cardiovascular risk reduction.[10]

The safety aspects of long-term therapy with Niaspan are quite promising, particularly when compared with other delayed-release formulations. Although there were small but significant effects on hepatic transaminases, uric acid, serum glucose, and other serum analytes, the vast majority of these changes occurred within the reference values for these analytes, have been observed with immediate-release niacin, and are unlikely to be clinically relevant. The changes in hematologic parameters were statistically significant and consistent only for platelets and leukocyte measurements; these changes, although small, warrant further observation. Of particular interest was the decrease in serum phosphorus levels (9% in this population), which was also observed with both Niaspan and immediate-release niacin during the earlier, placebo-controlled trials conducted in the course of the Niaspan Development Program (data on file, Kos Pharmaceuticals, Inc.). No side effects were associated with the decreases found in the Niaspan trials, but this new finding may provide further understanding of niacin action and, perhaps, its role in hepatic high-energy phosphate metabolism. The metabolic consequences of a mild drug-induced hypophosphotemia, and corrective modalities, pose intriguing biochemical questions and warrant further study.

Hepatic enzyme elevations above the upper limit of the reference ranges were exceedingly rare with long-term use of Niaspan, in this study, and were readily reversible with discontinuation of the drug. Although there may be differences in hepatic exposure to continuous levels of niacin and/or its metabolites that account for safety differences between Niaspan and various other preparations, it is likely that the Niaspan formulation is a major factor in its favorable therapeutic profile. Judging from the occurrence of greater hepatic safety issues raised in reports with various other formulations that delay the action of niacin, it is likely that most over-the-counter formulations would lead to a higher occurrence of hepatotoxicity and perhaps other side effects, if subjected to well-controlled clinical trials.

## CONCLUSIONS

These data clearly support the utility of Niaspan as a safe and effective serum lipoprotein-regulating agent for long-term use. Based on its general tolerability and once-nightly dosing regimen, it is expected that patient compliance will be greater with Niaspan than with other niacin preparations. Its long-term safety from clinical, biochemical, and hematologic standpoints suggest that Niaspan is safe and is unlikely to share the hepatotoxicity potential of other available extended-release preparations. Its therapeutic profile for potential efficacy in regulating all the key lipoprotein components of the various forms of dyslipidemia associated with premature coronary artery disease, including the atherothrombotic lipoprotein(a),[20] indicates that this agent will be a valuable therapeutic tool in the therapy of atherosclerosis. Future clinical trials of Niaspan, alone or in combination, will define its role in the therapy of heritable and sporadic lipid disorders and its utility in modifying various cardiovascular endpoints.

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