Extended-Release Niacin/Laropiprant: Reducing Niacin-Induced Flushing to Better Realize the Benefit of Niacin in Improving Cardiovascular Risk Factors

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KEYWORDS

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• Flushing • Laropiprant • Prostaglandin D_2

A substantial body of experimental, epidemiologic, and clinical trial data demonstrates that increased plasma low-density lipoprotein cholesterol (LDL-C) is associated with the progression of atherosclerotic coronary heart disease (CHD), and lowering LDL-C levels reduces CHD risk. Thus, reducing LDL-C levels remains the primary lipoprotein treatment target for reducing the risk of CHD.[1–3] Guidelines from regulatory bodies and expert panels have established different CHD risk categories and specific LDL-C treatment targets for each category.[1,4] Statin drugs are recommended as the initial therapy for lowering CHD risk, based on their LDL-C-lowering efficacy and favorable safety profile for most patients. Although relative risk reductions in major cardiovascular events

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from clinical outcomes trials of approximately 30% have been achieved with statin therapy, a substantial residual risk for clinical events (myocardial infarction [MI], coronary death, coronary revascularization, and stroke) remains for patients, even when well-treated for elevated LDL-C with a statin (**Table 1**), underscoring the need for therapies that target additional lipid risk factors.[5,6]

Vast experimental and epidemiologic data support an inverse association between HDL-C levels and CHD.[1,7] A meta-analysis of three clinical outcomes trials demonstrated that a 1 mg/dL higher level of HDL-C was associated with a 2% (men) or 3% (women) lower CHD risk.[7] Thus, raising HDL-C is a promising treatment target toward reducing CHD risk. HDL is hypothesized to participate in the transport of cholesterol from peripheral tissues (eg, that may be located in endothelial plaques) to the liver. Additionally, HDL may suppress vascular inflammation associated with atherosclerosis and have favorable antioxidative and antithrombotic effects.[8] In addition, several epidemiologic studies have provided evidence that elevated triglyceride (TG) levels are correlated with increased CHD risk.[9–12] This may be related, in part, to the inverse relationship between TG and HDL-C levels and the association between elevated TG levels and small dense low-density lipoproteins (LDL), which are believed to be especially atherogenic.

A joint statement released recently by the American Diabetes Association (ADA) and the American College of Cardiology (ACC) emphasizes the clinical importance of lipoprotein risk factors other than LDL-C in patients at high-risk for cardiovascular disease.[13] Citing evidence from epidemiologic studies and posthoc analyses of clinical trials that suggest non-HDL-C and Apo B are better predictors of cardiovascular risk than LDL-C, the ADA-ACC consensus statement recommended non-HDL-C goals of less than 100 and less than 130 mg/dL, respectively, and Apo B goals of less than 90 and less than 80 mg/dL, respectively, for high-risk patients without established heart disease and for highest risk patients who have heart disease or who have diabetes and other cardiovascular risk factors.[13]

NIACIN

Niacin (nicotinic acid) is a water-soluble B vitamin used to treat dyslipidemia for over 50 years.[14–16] Used in gram amounts, niacin has broad beneficial effects on the lipid profile, reducing plasma LDL-C and TG and increasing HDL-C levels.[17–19] The use of niacin and statin drugs together improves multiple key lipid/lipoprotein parameters known to impact CHD risk. Several clinical trials have shown that niacin produces cardiovascular benefit when used alone or together with statins (see **Table 1**).[20–22] The Coronary Drug Project, a large-scale placebo-controlled trial conducted between 1966 and 1975, demonstrated that niacin reduces CHD events: a 27% reduction in nonfatal MI and a 15% reduction in the combined endpoint of nonfatal MI and death were observed compared with placebo-treated patients.[20] A 15-year follow-up of the Coronary Drug Project revealed that patients in the niacin group had an 11% reduction in total mortality compared with those in the placebo group.[23] Two angiographic trials provided evidence that niacin coadministered with the bile acid sequestrant colestipol caused either regression or slowed progression of coronary stenosis or atherosclerosis.[24,25] Finally, in the HDL-Atherosclerosis Treatment Study (HATS), simvastatin plus slow-release niacin resulted in significant regression of coronary stenosis versus placebo and, consistent with this finding, a reduction in cardiovascular events.[21]

UNDERUTILIZATION OF NIACIN

Despite the acknowledged benefits in comprehensive lipid management and prevention of cardiovascular events, niacin is underutilized in clinical practice. A persistent, major impediment to the optimal use of niacin is the associated cutaneous flushing. Most patients who receive niacin, even at the 500 mg dose, experience flushing of the face and trunk.[26,27]

One approach to mitigate the flushing effects of immediate-release niacin, whose peak blood levels are attained 30 to 60 minutes after administration, has been through the development of niacin formulations that slow the release rate after oral administration.[28] Slow-release niacin has a dissolution time of over 12 hours and reduced flushing. Unfortunately, such agents are associated with increased hepatotoxicity. An extended-release (ER) niacin formulation (NIASPAN [Abbott Laboratories, North Chicago, IL] niacin ER tablets) has an absorption time (8 to 12 hours) between that of immediate-release and slow-release niacin and, as a result, reduced flushing compared with immediate-release niacin and an acceptable hepatic safety profile.[29,30] Amelioration of flushing with NIASPAN, however, requires a four-step, gradual titration regimen over 3 months to reach the efficacious 2 g dose. In the United States, patients begin with 0.5 g daily at bedtime and titrate the dose in 0.5 g increments every 4 weeks to 2 g. In the European Union and several Asian countries, the titration requires additional steps, initiating at

Table 1
Niacin and atherosclerosis: a positive effect on clinical outcomes

Trial	Study Population	Treatment (Mean Dose)	Number of Participants	Change in Lipids by Treatment Group					Findings
				PBO	T–C (%)	TG (%)	LDL-C (%)	HDL-C (%)	
CDP	Men (30–64 yrs) post-MI	Niacin (3 g/d)	1119	2789	↓ 10	↓ 19	NR	NR	↓ 27% Nonfatal MI All-cause mortality vs. placebo ↓ 11% Total mortality ($P = .0004$)
CLAS I	Men (40–59 yrs) post-CABG	Niacin (4.3 g/d) + colestipol (30 g/d)	80	82	↓ 26	↓ 21	↓ 43	↑ 37	Significant angiographic regression;
CLAS II	Men (40–59 yrs) post-CABG, 2-yr extension to CLAS I	Niacin (4.3 g/d) + colestipol (30 g/d)	56	47	↓ 25	↓ 18	↓ 40	↑ 37	Angiographic regression continued at 4 yrs
FATS	Men <65 yrs with high Apo B, CAD + history of VD	Niacin (4 g/d) + colestipol (30 g/d)	36	46	↓ 23	↓ 29	↓ 32	↑ 42	Significant angiographic regression ↓ 80% Clinical events[a] ($P < .01$)
HATS	Men/ women with CHD, low HDL-C	Niacin (2.4 g/d) + simvastatin (13 mg/d)	33	34	↓ 31	↓ 38	↓ 43	↑ 29	Significant angiographic regression ↓ 60%; clinical events[a] ($P = .02$)
Stockholm IHD	Men/ women post-MI	Niacin (3 g/d) + clofibrate (2 g/d)	279	276	↓ 13	↓ 19	NR	NR	↓ 36% ischemic heart disease mortality ($P < .01$); ↓ 26% total mortality ($P < .05$)
ARBITER 2	Men/ women with CHD + low HDL-C	ER Niacin (1 g/d) + ongoing statin	78	71	↓ 1	↓ 13	↓ 2	↑ 21	Slowed atherosclerosis progression at 12 months; no significant effect on CV events
ARBITER 3	Men/ women with CHD + low HDL-C completing ARBITER 2	ER niacin (1 g/d) + ongoing statin	57	–	NR	↓ 22	↓ 9	↑ 24	Additional slowing of atherosclerosis progression at 24 months

Abbreviations: ARBITER, Arterial Biology for the Investigation of Treatment Effects of Reducing Cholesterol; CABG, coronary artery bypass graft; CAD, coronary artery disease; CDP, Coronary Drug Project; CHD, coronary heart disease; CLAS, Cholesterol-Lowering Atherosclerosis Study; CV, cardiovascular; ER, extended release; FATS, Familial Atherosclerosis Treatment Study; HATS, Atherosclerosis Treatment Study; HDL, high-density lipoprotein; LDL, low-density lipoprotein MI, myocardial infarction; NR, not recorded; PBO, placebo; T–C, total cholesterol; TG, triglyceride; VD, vascular disease; vs, versus.

[a] Coronary death, stroke, revascularization, MI, worsening ischemia.

the 375 mg dose for the first week and titrating weekly to 500, 750, and 1000 mg in the fourth week. There is then further titration in 500 mg increments every 4 weeks up to 2 g at week 12.

Clinically meaningful lipid efficacy requires ER niacin doses of at least 1 g/d, and the 2 g/d dose provides twice the LDL-C reduction, twice the HDL-C elevation, and several times the TG reduction. However, the frequent ER niacin titration steps, along with persistent, episodic, bothersome, and unpredictable flushing episodes that sometimes have no obvious explanation limit dose escalation and patient acceptance and often lead to discontinuation of niacin therapy and the failure to achieve the optimal 2 g dose.

Three observational studies have elucidated the limitations in tolerability of ER niacin. These studies evaluated use and dosing patterns in clinical practice and the impact of flushing and other tolerability issues on suboptimal dosing and discontinuation.[31–34] The studies were conducted in the United States and Canada, where NIASPAN is the most frequently used prescription niacin formulation. Taken together, the results demonstrated poor persistency with ER niacin use and poor use of the 2 g dose in clinical practice, with flushing being the major reason.

The first study demonstrated in a chart review of clinical practices that at the 1-year time point after therapy initiation, only 14.6% of the original cohort of patients still filled prescriptions, the second highest discontinuation rate among lipid-modifying drug classes, second only to bile acid sequestrants (**Fig. 1**). Additionally, patients were not being titrated upwards to the efficacious lipid-altering doses. At 6 months, 39% of the patients persistent with ER niacin therapy still were receiving less than or equal to 500 mg/d (see **Fig. 1**),[31,32] a dose which offers little to no therapeutic benefit. At the end of the 1-year follow-up, only 5.8% of the original cohort took 1000 mg, and only 2.2% received more than 1500 mg.

The second study elucidated that flushing symptoms were the principal reasons given for discontinuation in about 91% of patients who discontinued ER niacin, and 54.4% experienced severe or extreme flushing.[33] In addition to flushing, other niacin-related adverse effects (ie, headache, gastrointestinal [GI] symptoms, insomnia) were described.

In the third study, patients initiating niacin therapy were interviewed prospectively about flushing symptoms.[34] Preliminary results demonstrated a trend consistent with the first retrospective observational study. At 6 months of follow-up, 53% still took 500 mg of ER niacin; 37% took 1 g, and only 2% took 2 g. The results also showed that the use of aspirin to reduce flushing was suboptimal, with regard to both the proportion of patients using aspirin and the dosage being used. Fewer than half of the patients using niacin received instruction from their physicians to use medication to mitigate flushing, and only 50% of those instructed actually used medication.

FLUSHING PATHWAY INHIBITION SUPPORTS A NEW NIACIN-DOSING REGIMEN

Although the mechanism by which niacin induces flushing is not understood completely, several lines of evidence suggest that flushing is mediated largely through prostaglandins, primarily PGD_2. First, predosing with aspirin (at doses of 325 mg and higher) or indomethacin, which inhibits synthesis of all prostanoids,[35] modestly attenuates niacin-induced flushing.[36–42] Second, plasma levels

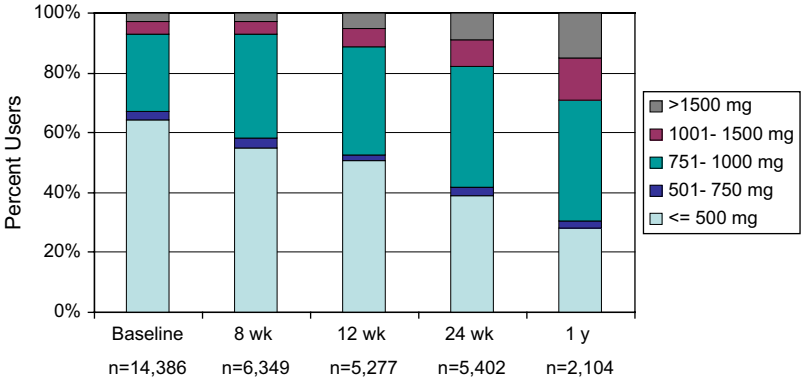

Fig. 1. Percentage of users of extended-release niacin at fixed time intervals by average daily dose. Includes patients with extended-release niacin prescription refills. Index prescription that identified patient's index date was recorded from a database as a 30-day supply. Sample size at baseline is therefore equal at 4 weeks (30 days). (*From* Kamal-Bahl S, Burke T, Watson D. Dosage, titration, and gaps in treatment with extended-release niacin in clinical practice. Curr Med Res Opin 2008;24:1819; with permission.)

of 9a, 11β-PGF_2, a metabolite of PGD_2, dramatically increases (430- to 800-fold) following a single oral dose of 500 mg niacin, peaking from 12 to 45 minutes after the dose and returning to baseline by 2 to 4 hours.[37] Importantly, niacin dosing does not increase histamine metabolites and modestly increases PGE_2[43,44] or a prostacyclin metabolite.[37] Third, intravenous infusion of PGD_2 is associated with intense facial flushing and nasal congestion.[45]

A study in a mouse model of niacin-induced vasodilation demonstrated that niacin-induced vasodilation is mediated in part by PGD_2 acting through one of the prostaglandin D type 1 receptors, called DP1.[46] Importantly, selective antagonism of DP1 with laropiprant produced significant dose-dependent suppression of PGD_2- and niacin-induced vasodilation.[46] Taken together, these observations suggest that blockade of the PGD_2 receptor, specifically the subtype 1 (DP1), may suppress the flushing symptoms associated with niacin. Moreover, although the flushing effects of niacin are mediated by the niacin receptor, they appear to be independent of the lipid-modifying effects of niacin.[14]

LAROPIPRANT

Laropiprant, a selective antagonist of DP1 (Ki 0.57 nM and 190-fold less potent at the thromboxane A2 receptor, TP), was examined in a series of clinical studies to determine its ability to reduce flushing and improve the tolerability of niacin. A clinical proof-of-concept study demonstrated that laropiprant significantly suppressed vasodilation induced by ER niacin and improved patient-reported flushing symptoms (using a rudimentary 11-point symptom severity scale) to a degree greater than that provided by aspirin before treatment.[47] The symptomatic improvement with laropiprant correlated with a reduction in the skin vasodilation induced by ER niacin, as quantitated with laser Doppler perfusion imaging.[47] Laropiprant was tolerated well, having been studied alone or coadministered with niacin in long-term preclinical animal chronic toxicity studies, as well as clinical pharmacology multiple-dose studies using up to 10 times the exposure used in subsequent human studies.[47]

MEASURING NIACIN-INDUCED FLUSHING: THE FLUSHING SYMPTOM QUESTIONNAIRE

Existing tools that report flushing adverse experiences and discontinuations were not considered sufficiently objective, precise, or robust to support a rigorous clinical development program. Thus, a quantitative Flushing Symptom Questionnaire (FSQ, Merck & Company, Incorporated, Whitehouse Station, New Jersey) was developed that consisted of an 11-item diary, assessing aspects of the frequency, severity, duration, and bother of niacin-induced flushing (including symptoms of redness, warmth, tingling, and/or itching).[48] The content of the FSQ was developed with input from patients taking niacin and clinicians experienced in treating patients with niacin to address four key objectives:

1. Accurately measure the magnitude and severity of niacin-induced flushing
2. Define the key treatment windows/endpoints in which niacin use is problematic to patients and for which a flushing pathway inhibitor provides value
3. Quantify the response to therapy and improvements in tolerability.
4. Provide a measure sufficiently precise and robust to support the requirements of dose-ranging and clinical impact studies

In addition to the questions that characterized the individual flushing symptoms (redness, warmth, itching, and tingling), a question of the FSQ, termed the Global Flushing Severity Score (GFSS), assessed aggregated flushing severity of all four symptoms (Overall, during the past 24 hours, how would you rate your flushing symptoms? [including redness, warmth, tingling, or itching of your skin] 0 = did not have, 1–2 = mild, 4–6 = moderate, 7–9 = severe, 10 = extreme). The FSQ items concerning the severity, bother, and individual flushing symptoms use a discretized analog response scale that combines both verbal descriptors and a 0 to 10 numerical rating, key design elements shared with other well-validated disability measures.[49]

A validation study was conducted to determine the most appropriate endpoints for assessing niacin-induced flushing associated with initiation and maintenance of therapy.[48] The results supported the measurement properties and validity of the FSQ. The GFSS item alone performed as well as or better than the four individual flushing symptoms. Finally, this study identified two specific time periods (and efficacy endpoints) of interest to measure niacin-induced flushing: the initiation phase (maximum GFSS during the first week of therapy) and maintenance phase (frequency of moderate or greater flushing during chronic 2 g dosing).

LAROPIPRANT IN PHASE II

Based on the validation data, the FSQ, administered by means of an eDiary (ie, patient

self-reported flushing symptoms recorded in a PalmPilot device), was employed in Phase II to quantify the effects of ER niacin/laropiprant on niacin-induced flushing.[50] An 8-week, placebo-controlled, parallel group study was designed to determine the dose–response relationship of laropiprant-mediated inhibition of flushing during the initiation phase of treatment (week 1) and during the maintenance phase (defined as weeks 6 to 8 for this study) using the FSQ eDiary GFSS question.[50] Patients were randomized to NIASPAN 1 g alone (used as a formulation of ER niacin available at the time) or coadministered with laropiprant 18.75 to 150 mg or double placebo. After 4 weeks, all doses were doubled to achieve 2 g niacin and laropiprant 37.5 to 300 mg for an additional 4 weeks.

Coadministration of laropiprant with NIASPAN produced a significant reduction in niacin-induced flushing compared with ER niacin alone in dyslipidemic patients at initiation of treatment (**Fig. 2**) and with chronic maintenance of therapy. The beneficial effects of niacin on lipids were not affected. In this first study, all laropiprant doses were sufficient to significantly attenuate flushing with the 1 g initiation dose of niacin and the 2 g maintenance dose.

Laropiprant administered at 37.5 mg (rounded to 40 mg and given as two 1 g/20 mg tablets) was found to be the minimum dose that maximally protects against flushing associated with the expected patterns of chronic use of niacin at the 2 g dose (compliant use and after missed doses). Similarly, the amount of laropiprant in the single 1 g tablet (20 mg) provides maximum protection against the flushing associated with the one-tablet starting dose of 1 g niacin (to be given as 1 g/20 mg).

Selection of an ER niacin formulation (Merck & Company, Incorporated) to be combined with laropiprant was based on various assessments, including pharmacokinetic profile, pharmaceutical properties, flushing profile (intrinsic flushing and response to laropiprant), lipid-altering efficacy, and safety/tolerability. The new ER niacin formulation demonstrated an acceptable safety and tolerability profile, with efficacy comparable to that of NIASPAN on HDL-C, LDL-C, and TG at the 2 g dose.

The results of the dosing and formulation studies culminated in the development of ER niacin/laropiprant, a combination agent aimed at providing the beneficial lipid-modifying effects of niacin, while offering improved tolerability. A two-step dose advancement regimen (1 g/20 mg for 4 weeks followed by 2 g/40 mg for chronic maintenance) was selected for subsequent studies of ER niacin/laropiprant. This new dosing regimen overcomes the limitations inherent in the 12-week gradual dose titration regimen believed to be a critical impediment to achieving the optimal 2 g dose with currently available ER niacin formulations. ER niacin/laropiprant ensures that patients receive a minimally therapeutic 1 g dose of niacin at the

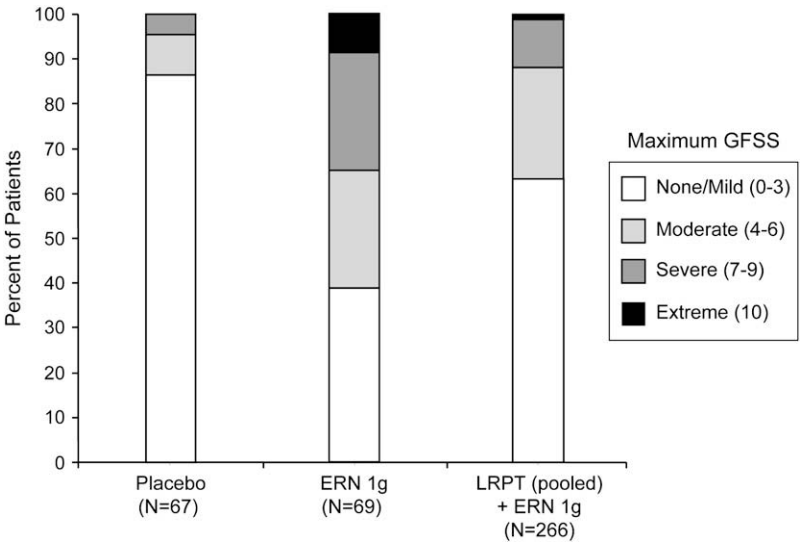

Fig. 2. Maximum Global Flushing Severity Score (GFSS) in week 1 in study 011, presented as percent of patients. *Abbreviations:* ERN, extended-release niacin; GFSS, Global Flushing Severity Score; LRPT, laropiprant. (*From* Paolini JF, Mitchel YB, Reyes R, et al. Effects of laropiprant on nicotinic acid-induced flushing in dyslipidemic patients. Am J Cardiol 2008;101:626; with permission.)

initiation of therapy, an important advance considering that 500 mg NIASPAN is a titration dose with nonsignificant LDL-C-lowering and that approximately one third of patients never titrate upward beyond 500 mg.[31]

PHASE III CLINICAL STUDIES WITH LAROPIPRANT

Two distinct sets of efficacy endpoints were evaluated in the ER niacin/laropiprant Phase III program: those related to lipid effects and those related to reducing niacin-induced flushing at initiation and with chronic maintenance of therapy. Another equally important objective of these studies was the assessment of the safety and tolerability profile of ER niacin/laropiprant, particularly with regard to the novel 1 g starting dose and the 1g → 2 g dose advancement regimen.

EFFECTS ON LIPIDS

Two pivotal Phase III clinical trials (studies 020 and 022) evaluated the lipid efficacy of ER niacin/laropiprant,[51,52] with the primary lipid endpoint being the percent change from baseline in LDL-C levels. In a randomized, placebo-controlled study (020), dyslipidemic patients (67% on statins) were randomized to ER niacin/laropiprant (n = 800), ER niacin (n = 543), or placebo (n = 270). Treatment with ER niacin/laropiprant and ER niacin was initiated at 1 g. After 4 weeks, the dose was advanced to 2 tablets per day (2 g for active treatment) for 20 additional weeks. ER niacin/laropiprant 2 g/40 mg produced significant and durable reductions in plasma LDL-C levels (−18.4%) relative to placebo in the overall study population (**Table 2**). Importantly, the LDL-C lowering efficacy of ER niacin/laropiprant was similar whether it was administered as monotherapy (ie, without statin background treatment, −17.4%) or as combination therapy with statins (−18.9%). These similarities in LDL-C lowering with or without previous statin therapy were observed despite the large differences in baseline LDL-C levels in these two subgroups (approximately 95 vs. approximately 150 mg/dL; this difference was expected due to disparity in enrollment criteria based on statin use and risk category). Similarly, baseline HDL-C and TG levels did not influence the LDL-C lowering efficacy of ER niacin/laropiprant. Finally, the lipid effects of ER niacin/laropiprant and ER niacin were nearly identical, confirming earlier observations that laropiprant alone does not affect lipid levels.

The results of Study 020 generally were corroborated in a factorial study designed to evaluate the lipid-modifying efficacy of ER niacin/laropiprant plus simvastatin, compared with the monotherapy of each (Study 022). After a 6- to 8-week washout and a 4-week diet/placebo run-in, 1398 patients were randomized equally to ER niacin/laropiprant 1 g/20 mg, simvastatin (10, 20, or 40 mg), or ER niacin/laropiprant 1 g/20 mg plus simvastatin (10, 20, or 40 mg) once daily for 4 weeks. At week 5, treatment doses were doubled in all groups except simvastatin 40 mg (unchanged) and ER niacin/laropiprant 1 g/20 mg plus simvastatin 40 mg (switched to ER niacin/laropiprant 2 g/40 mg plus simvastatin 40 mg). Significantly larger reductions in LDL-C levels were evident with the coadministration of ER niacin/laropiprant 2 g/40 mg plus simvastatin (pooled across simvastatin doses of 20 mg and 40 mg) compared with ER niacin/laropiprant or simvastatin (pooled across simvastatin doses of 20 mg and 40 mg) (**Table 3**). In addition, when evaluating the lipid effects of ER niacin/laropiprant 2 g/40 mg plus simvastatin, all individual dose comparisons were significantly different from the respective monotherapy doses.

Table 2
Lipid efficacy from study 020

Least Squares Mean (95% CI) % Change from Baseline in Lipids Across Weeks 12 Through 24[a]			
Lipid Parameter	**Extended Early Release Niacin/Laropiprant 2 g**	**Placebo**	**Difference**
Low-density lipoprotein (LDL)−C	−18.9 (−21.0, −16.8)	−0.5 (−3.3, 2.4)	−18.4 (−21.4, −15.4)
High-density lipoprotein (HDL)−C	18.8 (17.2, 20.4)	−1.2 (−3.4, 1.0)	20.0 (17.7, 22.3)
Triglycerides, median	−21.7 (−23.9, −19.5)	3.6 (−0.5, 7.6)	−25.8 (−29.5, −22.1)
Non HDL−C	−19.0 (−20.8, −17.2)	0.8 (−1.6, 3.3)	−19.8 (−22.4, −17.3)
Apo B	−16.4 (−18.0, −14.7)	2.5 (0.2, 4.7)	−18.8 (−21.2, −16.5)
Apo AI	11.2 (10.1, 12.4)	4.3 (2.7, 5.9)	6.9 (5.3, 8.6)

[a] Patients with at least one post-titration measurement included in the analysis.

Table 3
Lipid efficacy from study 022

Least Squares Mean Percent Changes in Lipid Parameters from Baseline to Week 12			
Treatment Group	**LDL−C**	**TG[a]**	**HDL−C**
ER niacin/laropiprant 2 g/40 mg	−17.0	−21.6	23.4
Simvastatin 20 mg	−34.7	−13.4	4.2
Simvastatin 40 mg	−38.2	−15.1	6.8
Pooled simvastatin 20 and 40 mg	−37.0	−14.7	6.0
ER niacin/laropiprant 2 g/40 mg + simvastatin 20 mg	−45.7[b,e]	−30.9[b,e]	27.7[c,e]
ER niacin/laropiprant 2 g/40 mg + simvastatin 40 mg	−48.9[b,e]	−33.6[b,e]	27.4[c,e]
Pooled ER niacin/laropiprant 2 g/40 mg + simvastatin	−47.9[b,d]	−33.3[b,d]	27.5[c,d]

Abbreviations: ER, extended release; HDL−C, high-density lipoprotein cholesterol; LDL−C, low-density lipoprotein cholesterol; TG, triglycerides.
[a] Expressed as median percent change.
[b] $P < .001$ versus ER niacin/laropiprant.
[c] $P < .050$ versus ER niacin/laropiprant.
[d] $P < .001$ versus pooled simvastatin.
[e] $P < .001$ versus corresponding dose of simvastatin alone.

In both studies, the kinetics of the response showed a tendency for the LDL-C lowering to plateau after 8 to 12 weeks of treatment (4 to 8 weeks at 2 g) and remain stable for the duration of the studies (12 to 24 weeks). Significant effects of ER niacin/laropiprant 1 g/20 mg alone or coadministered with simvastatin also were observed at the 4-week time point.

Although niacin is effective at reducing LDL-C levels, it also effectively raises HDL-C. In the factorial study (Study 022), ER niacin/laropiprant produced significant increases of 23% to 28% in HDL-C, whether administered alone or with simvastatin (see **Table 3**). These effects were observed irrespective of baseline LDL-C, HDL-C, or TG levels. Similar increases in HDL-C also were observed in Study 020.

Reductions in TG levels followed a similar pattern to the beneficial changes in LDL-C and HDL-C with ER niacin/laropiprant alone or coadministered with simvastatin, producing significantly larger reductions than the individual components (see **Table 3**).

Overall, the treatment effects of ER niacin/laropiprant on lipid parameters observed in the phase III studies were consistent across patient subgroups, including those defined by age, gender, race, baseline lipid values (high and low LDL-C, HDL-C, and TG), and diabetes mellitus status. Consistent treatment effects also were observed across subgroups of patients on different types of statins (simvastatin, atorvastatin, or other statins) and in patients taking statins and ezetimibe concomitantly.

EFFECTS ON NIACIN-INDUCED FLUSHING

Prespecified endpoints in the phase III studies evaluated the flushing profile of ER niacin/laropiprant during initiation of therapy when flushing is believed to be most intense and during chronic maintenance therapy when patients may experience intermittent, sometimes unpredictable flushing. These studies also assessed the tolerability of the abbreviated 1 g → 2 g dosing regimen of ER niacin/laropiprant relative to the 12-week gradual titration regimen of NIASPAN in a head-to-head study (Study 054), in which the use of aspirin was permitted to mitigate flushing symptoms.

The initiation phase is defined as the first week of niacin treatment, and the maintenance phase refers to the period after the first week of treatment, including the period after patients advance to the maintenance dose (2 g/40 mg of ER niacin/laropiprant or 2 g of niacin). In each study, ER niacin/laropiprant (administered according to the 1 g → 2 g dosing regimen) was compared with ER niacin alone, either according to the same 1 g → 2 g regimen (using Merck's ER niacin formulation) or to the usual regimen of conservative titration, starting at 500 mg and increasing in 500 mg increments every 4 weeks until reaching the 2 g dose (using NIASPAN).

INITIATION OF THERAPY AND ADVANCEMENT TO 2 G MAINTENANCE DOSE

The ability of laropiprant to mitigate flushing associated with the initiation of therapy was a primary

objective in Study 020. ER niacin/laropiprant and ER niacin were administered according to the simplified ER niacin/laropiprant dosing regimen (a 1 g initial dose advanced to 2 g after 4 weeks). During the initiation of therapy (week 1), patients treated with ER niacin/laropiprant experienced significantly less flushing than did patients receiving ER niacin, as measured by the distribution of patients experiencing maximal flushing across the intensity categories of none/mild, moderate, severe, and extreme. Overall, fewer patients experienced moderate, severe, or extreme flushing with ER niacin/laropiprant 1 g versus ER niacin 1 g during week 1 (31% vs. 56%; $P < .001$), with a 65% reduction in the odds of experiencing such flushing. Similarly, fewer patients experienced severe or extreme flushing with ER niacin/laropiprant versus ER niacin (14% vs. 33%, $P < .001$). These results provide support for the concept of using an abbreviated dosing regimen with ER niacin/laropiprant, in which the starting dose is 1 g of ER niacin.

MAINTENANCE PHASE

On the basis of anecdotal reports, it has been ascertained that people develop tolerance with compliant dosing of niacin. An important objective of the ER niacin/laropiprant development program was to rigorously assess the chronic flushing response to niacin in a long-term study, by the objective use of a validated flushing tool. In Study 020, patients in the ER niacin/laropiprant and ER niacin groups remained at the 2 g dose for 20 weeks of treatment, making this study ideal for assessing flushing with therapy maintenance. After week 6, patients treated with ER niacin continued to report episodes of moderate, severe, or extreme flushing, while the flushing signal in patients treated with ER niacin/laropiprant gradually subsided to a level that approximated placebo. During the maintenance phase, the ER niacin/laropiprant group experienced significantly less flushing than the ER niacin group as measured by days per week with moderate or greater flushing, and the difference was consistent throughout the entire 24-week treatment period. At the end of the treatment period, patients in the ER niacin/laropiprant group had 0.2 days per week with moderate, severe, or extreme flushing versus 0.7 days per week in the ER niacin group (approximately 1 day per month vs. approximately 1 day per week, respectively). This flushing profile was not driven by a minority of patients experiencing high degrees of flushing; rather, approximately 60% of patients receiving ER niacin 2 g reported at least one episode of moderate or greater flushing throughout the period between weeks 6 and 24. These data show that moderate or greater flushing is persistent in a large percentage of patients and that tolerance to this level of flushing is incomplete over at least a 6-month period. This is consistent with data illustrating a high rate of discontinuation from ER niacin use because of flushing over 1 year.[32]

COMPARISON WITH GRADUALLY TITRATED NIASPAN

NIASPAN typically is titrated gradually over a 12-week period in an attempt to address dose-related flushing symptoms. Thus, a phase III, head-to-head study (Study 054) was conducted to assess the novel 1 g → 2 g ER niacin/laropiprant abbreviated dosing regimen compared with NIASPAN. Each treatment was administered for 16 weeks, according to its standard dosing regimen. ER niacin/laropiprant 1 g was given for 4 weeks then advanced to 2 g for the remaining 12 weeks. NIASPAN 0.5 g was given for 4 weeks, then increased every 4 weeks in 0.5 g increments to 2 g for the final 4 weeks. Patients were instructed to take study therapy in the evening with food. According to the discretion of the patient, preadministration of aspirin (or other nonsteroidal anti-inflammatory drugs [NSAIDs]) 30 minutes before study medication was allowed to specifically mitigate flushing symptoms.

Patients treated with rapidly advanced ER niacin/laropiprant experienced significantly ($P < .001$) less flushing than those treated with gradually titrated NIASPAN, as measured by the number of days per week with moderate, severe, or extreme flushing (GFSS greater than or equal to 4) across the treatment period categorized as 0, greater than 0 and less than or equal to 0.5, greater than 0.5 and less than or equal to 1, greater than 1 and less than or equal to 2, greater than 2 and less than or equal to 3, and greater than 3 days per week. Overall, more than twice as many patients had no episodes of moderate, severe, or extreme flushing (GFSS greater than or equal to 4) with ER niacin/laropiprant versus NIASPAN (47% vs. 22%, respectively) across the 16-week treatment period. Importantly, clinically significant changes were identified across the entire scale, not only categorically but also numerically, and without the need for specific GFSS cut points.

The time profile of flushing across the entire treatment period was evaluated by means of by-week plots of the following: the number of days per week with moderate, severe, or extreme flushing in each week, and the percentage of patients who had moderate, severe, or extreme flushing in each week (**Fig. 3**). Despite the dose of ER

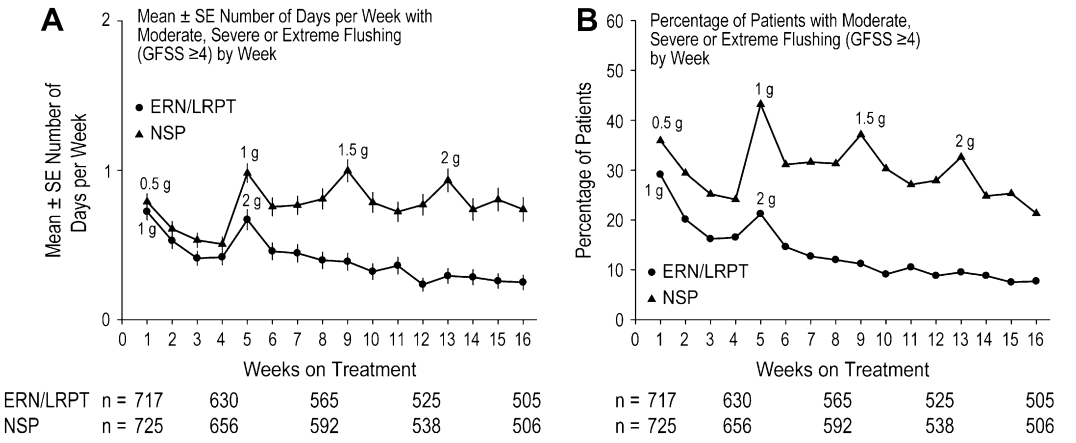

Fig. 3. Time profile of flushing in study 054: (*A*) Mean ±SE days per week with moderate, severe, or extreme flushing (GFSS greater than or equal to 4), by week. (*B*) Percentage of patients with moderate, severe, or extreme flushing (GFSS greater than or equal to 4), by week. *Abbreviations:* ERN, extended-release niacin; GFSS, Global Flushing Severity Score; LRPT, laropiprant; NSP, NIASPAN.

niacin/laropiprant (1 g) being double that of NIASPAN (0.5 g) during the first 4 weeks, the groups were similar with regard to the number of days per week with moderate, severe, or extreme flushing. Although the flushing signal gradually declined after week 5 in the ER niacin/laropiprant group, it remained elevated in the group treated with NIASPAN, with increases in the signal at each titration week. ER niacin/laropiprant patients experienced fewer days per week with moderate, severe or extreme flushing relative to NIASPAN at the end of the treatment period. In addition, a lower percentage of patients had maximum GFSS reported as moderate, severe, or extreme at week 5 in the ER niacin/laropiprant group versus the group treated with NIASPAN (21.2% vs. 43.2%, respectively). The percentage of patients who had maximum GFSS reported as moderate, severe, or extreme at week 16 was 7.7% for the ER niacin/laropiprant group versus 21.3% for the group treated with NIASPAN.

These results indicate that laropiprant can reduce the intrinsic flushing signal of a 1 g ER niacin dose to less than that of a 0.5 g dose of NIASPAN. The tolerability differences not only persisted for the duration of the study but actually grew larger during the ensuing weeks of the study. Whereas the patients who continued to titrate up on NIASPAN experienced a high level of flushing and spikes in the flushing signal with each dose titration step, patients in the ER niacin/laropiprant group who reached the 2 g dose by week 5 experienced a progressive decrease in the frequency of flushing symptoms. By week 8, patients in ER niacin/laropiprant group were receiving near-maximal lipid-altering benefits at the 2 g dose, with fewer than 10% of these patients experiencing moderate, severe, or extreme (GFSS greater than 4) flushing symptoms.

Importantly, superiority of the 1 g → 2 g ER niacin/laropiprant dosing regimen was observed in the setting of patients having the option of taking aspirin or NSAIDs to help alleviate flushing symptoms. Whereas aspirin modestly reduces flushing symptoms with niacin monotherapy, it does not provide additional benefit beyond that of laropiprant in patients receiving ER niacin/laropiprant.[53] Not only did more patients in the group treated with NIASPAN use aspirin/NSAIDs to mitigate flushing symptoms (21.6% vs. 11.3%), but only the patients treated with NIASPAN would have seen any decrease in flushing scores as a result of its use.

These data show that the improvement in flushing symptoms that the laropiprant component provides is sufficiently robust to yield a superior tolerability profile for ER niacin/laropiprant, even with an accelerated 1 g → 2 g dose advancement regimen. The improved tolerability of ER niacin/laropiprant persists, even when compared with the recommended gradual titration schedule of NIASPAN, with the discretionary use of aspirin and/or other NSAIDS.

DISCONTINUATION BECAUSE OF FLUSHING

The clinical significance of the reduction in flushing provided by laropiprant is underscored by the finding that consistently fewer patients discontinued from ER niacin/laropiprant therapy because of flushing symptoms than comparator niacin formulations. The percentage of patients discontinuing because of flushing was a key secondary endpoint

in the placebo-controlled study (Study 020) and an exploratory endpoint in the head-to-head study (Study 054). In Study 020, 10% in the ER niacin/laropiprant and 22% in the ER niacin groups discontinued because of flushing over the 6-month study ($P < .001$). Corresponding rates for groups treated with ER niacin/laropiprant or NIASPAN in Study 054 were 7% and 12% over 16 weeks of treatment, demonstrating superiority with ER niacin/laropiprant, even though patients in the ER niacin/laropiprant group were at a higher dose of niacin for all but the last 4 weeks of the study. This is noteworthy given the short duration of the clinical trials and the inherent encouragement for patients not to discontinue (patients were encouraged strongly to stay in the trials and endure their flushing symptoms rather than discontinue, if possible). Although it is difficult to predict real-world discontinuation rates from clinical trials, one reasonably could presume that the discontinuation rates might have been even higher had these patients not been as highly motivated and encouraged to remain in the studies, as is the case within the unique environment of a controlled clinical trial. Observational studies have shown that approximately 85% of patients discontinue niacin over 12 months, and most cite flushing as the reason.

SAFETY

Data were pooled from three active- or placebo-controlled phase III studies and three, phase II, 1-year safety extensions. The results indicate that ER niacin/laropiprant generally was tolerated well. Apart from the clear advantage of ER niacin/laropiprant on flushing-related adverse events and discontinuations, the tolerability profile of ER niacin/laropiprant was similar to that of ER niacin alone (**Table 4**).

The overall population was comprised of 4747 patients exposed to ER niacin/laropiprant (n = 2548), ER niacin/NIASPAN (n = 1268), or simvastatin/placebo (n = 931). The studies ranged from 12 to 52 weeks in duration. The incidence of consecutive greater than or equal to three times the upper limit of normal (ULN) increases in alanine aminotransaminase (ALT) and/or aspartate aminotransferase (AST) was low and similar across the groups. Elevations were reversible with therapy discontinuation and not associated with clinical hepatotoxicity. There was no evidence that ER niacin/laropiprant had an adverse effect on muscle. There were two cases of myopathy, defined as creatine kinase greater than or equal to 10 times ULN with muscle symptoms and considered

Table 4
Extended-release niacin/laropiprant safety summary

Safety Parameter	Simvastatin/Placebo	Extended-Release Niacin	Extended-Release Niacin/Laropiprant
Drug-related[a] adverse events, n/N (%)	156/931 (16.8)	501/1268 (39.5)	901/2548 (35.4)[d,e]
Drug-related[a] serious adverse events, n/N (%)	1/931 (0.1)	1/1268 (0.1)	8/2548 (0.3)[f,g]
Discontinuations due to drug−related[a] adverse events, n/N (%)	28/931 (3.0)	204/1268 (16.1)	328/2548 (12.9)[d,e]
Confirmed adjudicated cardiovascular events, n/N (%)	3/931 (0.32)	5/1268 (0.39)	8/2548 (0.31)[h,i]
Consecutive ALT/AST elevations $\geq 3\times$ ULN, n/N (%)	8/920 (0.9)	6/1221 (0.5)	25/2465 (1.0)[h,i]
Drug-related hepatitis, n/N (%)	0/920 (0.0)	0/1221 (0.0)	0/2465 (0.0)
Myopathy,[b] n/N (%)	0/920 (0.0)	1/1221 (0.08)	1/2465 (0.04)[h,i]
CK elevations $\geq 10 \times$ ULN, n/N (%)	2/920 (0.2)	2/1221 (0.2)	7/2465 (0.3)[h,i]
New-onset diabetes,[c] n/N (%)	1/888 (0.1)	3/1094 (0.3)	12/2276 (0.5)[h,i]

Abbreviations: ALT/AST, alanine aminotransferase and/or aspartate aminotransferase; CK, creatine kinase;ER, extended release; n, number of patients with given event; N, total patients in treatment group; ULN, upper limit of normal.

[a] Determined to be possibly, probably, or definitely drug-related by the investigator.
[b] CK$\geq 10 \times$ ULN with muscle symptoms and considered drug-related by the investigator.
[c] Based on clinical adverse events and change in medication.
[d] 95% CI for difference with ER niacin does not include 0.
[e] 95% CI for difference with simvastatin/placebo does not include 0.
[f] 95% CI for difference with ER niacin includes 0.
[g] 95% CI for difference with simvastatin/placebo includes 0.
[h] Not significantly different from ER niacin.
[i] Not significantly different from simvastatin/placebo.

drug-related by the investigator: one each in the ER niacin (0.08%) and ER niacin/laropiprant (0.04%) groups. Both were associated with unusually high levels of physical activity. ER niacin/laropiprant and ER niacin produced small increases in fasting blood glucose levels (approximately 4 mg/dL median change from baseline), consistent with the known effects of niacin. Very few patients in the pooled population met a prespecified criterion for new-onset diabetes (a clinical adverse event of diabetes mellitus or initiation of antidiabetic medication), and there were no significant differences between the treatment groups receiving ER niacin versus placebo. Overall, there was no difference between the treatment arms with respect to the incidence of confirmed cardiovascular events, although no study to date has been sufficient in power or duration to establish any potential cardiovascular differences. The magnitude of potential benefits of ER niacin/laropiprant on cardiovascular outcomes and atherosclerosis is being assessed in the ongoing 4-year, 20,000-patient clinical outcome study, the Heart Protection Study–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE). The favorable safety and tolerability profile of ER niacin/laropiprant for up to 12 months supports the use of laropiprant to achieve the optimal therapeutic dosing of niacin, an agent shown to reduce cardiovascular risk.

SUMMARY

ER niacin/laropiprant produces superior lipid-altering efficacy relative to placebo, whether administered as monotherapy or coadministered with concomitant statin. Coadministration of ER niacin/laropiprant with simvastatin was highly efficacious at producing beneficial changes across the lipid profile. The lipid effects of ER niacin/laropiprant 2 g/40 mg were maintained over 52 weeks of treatment.

Laropiprant consistently mitigates niacin-induced flushing, as measured by objective, validated measures of flushing. Given that difficulties with flushing tolerability and the necessary 12-week gradual dose titration regimen remain critical impediments to achieving the target 2 g dose with currently available ER niacin formulations, combining an inhibitor of the flushing pathway with ER niacin supports a fundamental change in the niacin dosing paradigm. Replacing the standard gradual, multistep ER niacin titration regimen with a more streamlined and better-tolerated regimen may allow patients to successfully initiate treatment at the 1 g dose and more rapidly advance to the 2 g target dose, with accompanying improvement in compliance and adherence. Treatment with ER niacin/laropiprant generally was tolerated well, and with the exception of flushing-related adverse events, which occurred more frequently with ER niacin, had a safety profile similar to that of ER niacin. In July 2008, ER niacin/laropiprant was approved for marketing in the European Union, Iceland and Norway.

In conclusion, ER niacin/laropiprant offers the opportunity for a major therapeutic advance. The improvements in the tolerability of niacin observed with ER niacin/laropiprant will allow niacin dosing to initiate therapy at a therapeutic 1 g dose and rapidly advance to the maximum efficacious 2 g dose in a simplified dosing regimen. ER niacin/laropiprant is a generally well-tolerated and easy-to-use, long-term treatment for dyslipidemia that offers the potential for more patients to realize the demonstrated lipid-altering and cardiovascular benefits of niacin, a therapy proven to reduce cardiovascular risk.

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