Efficacy and safety of extended-release niacin/laropiprant in patients with type 2 diabetes mellitus

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Cardiovascular disease is a major cause of death in patients with type 2 diabetes mellitus (T2DM) and multiple lipid abnormalities are common. Niacin effectively treats diabetic dyslipidaemia and reduces cardiovascular events in high-risk patients. We evaluated the lipid-altering efficacy and safety (especially, glycaemic control) of extended-release niacin/laropiprant (ERN/LRPT; a tablet containing 1 g ERN and 20 mg LRPT) in patients with T2DM. In this multi-centre, double-blind, placebo-controlled, 36-week study, patients (n=796) were randomised 4:3 to ERN/LRPT or placebo. After four weeks at 1 g/day, ERN/LRPT was doubled to 2 g/day (two tablets) for the remainder of the study. The vast majority of randomised patients (~90%) were dyslipidaemic based on medical history or baseline lipid levels; approximately 80% were taking statins and 99% were on an antihyperglycaemic regimen.

At week 12, ERN/LRPT produced significant (p≤0.001 for all) percentage changes from baseline in low-density lipoprotein cholesterol (LDL-C) (–17.9%), high-density lipoprotein cholesterol (HDL-C) (23.2%), LDL-C:HDL-C (–32.0%), triglycerides (–23.1%), apolipoprotein (Apo) B (–17.1%), Apo A-I (8.2%) and total cholesterol (TC):HDL-C (–22.9%) versus placebo. The clinical and laboratory adverse events that occurred more frequently in the ERN/LRPT group versus the placebo group were pruritus, rash, flushing, gastrointestinal upset and elevations in alanine aminotransferase, aspartate aminotransferase, fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA_{1c}). From baseline to week 36, median FPG and HbA_{1c} increased with ERN/LRPT from 7.31 to 7.88 mmol/L and 6.9 to 7.3%, respectively, consistent with known niacin effects. More patients in the ERN/LRPT group required intensified antihyperglycaemic therapy (17.6% *vs.* 8.2%; p≤0.001). In this population of patients with T2DM, ERN/LRPT produced significant, durable improvements in lipids/lipoproteins and had a safety profile consistent with ERN/LRPT and ERN alone in other populations.

Key words

extended-release niacin/laropiprant, fasting plasma glucose, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol, triglycerides, type 2 diabetes mellitus

Introduction

Patients with type 2 diabetes mellitus (T2DM) have a two- to four-fold increased risk for cardiovascular disease (CVD) compared with individuals without T2DM.[1] A dyslipidaemia pattern of increased levels of triglyceride (TG)-rich particles, and TG enrichment of high- and low-density lipoprotein (HDL and LDL) is common in patients with T2DM, affecting nearly all lipid and lipoprotein variables.[2] As a result, dyslipidaemia in patients with T2DM is characterised by elevated TG levels, low HDL-cholesterol (HDL-C) levels, and a preponderance of small, dense LDL particles. Thus, while current guidelines primarily focus on lowering total cholesterol (TC) and LDL-cholesterol (LDL-C) to reduce CVD risk, consideration of HDL-C and TG levels as secondary treatment targets is also important among high-risk patients, including those with T2DM.[1,3-5]

Treatment with 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors (statins) produces significant improvements in plasma LDL-C levels among patients with T2DM.[6,7] Patients with T2DM are at high CVD risk and require intensive treatment of multiple lipid

parameters. In high-risk patients, lipid treatment goals are frequently not attainable with statin monotherapy, therefore, additional lipid-altering drugs are often required to optimise CVD risk reduction.

Niacin (nicotinic acid) raises HDL-C levels, lowers LDL-C, TG and lipoprotein(a) (Lp[a]) levels, and reduces atherogenic small, dense LDL particles.[3,8] Niacin, at doses ≥2 g/day, administered alone or in combination with other lipid-modifying therapies, reduces atherosclerotic coronary heart disease (CHD) and may reduce coronary events in patients with CVD.[9-13] However, the clinical use of niacin is often hampered by poor tolerability.[14,15] Niacin is sometimes associated with gastrointestinal side effects and can increase liver transaminases, uric acid, and fasting plasma glucose (FPG), which at times may necessitate modification of antihyperglycaemic therapy and/or reduction/withdrawal of niacin therapy.

Flushing (defined as redness, warmth, itching and tingling of the skin) is one of the major limitations to the sustained use of efficacious niacin doses.[16-20] Niacin-induced flushing is mediated primarily by prostaglandin D_2 (PGD_2), which stimulates PGD_2 receptor-1 (DP1) in the skin.[21] Laropiprant (LRPT) is a potent, once-daily, highly selective DP1 antagonist that reduces the incidence and intensity of niacin-induced flushing.[22,23] Clinical trial data support the efficacy and safety of a fixed-dose combination tablet of LRPT and extended-release niacin (ERN; Merck & Co., Inc.), designated ERN/LRPT, in dyslipidaemic patients. Due to decreased flushing, ERN/LRPT does not require the multiple-step, incremental up-titration common for ERN. Rather, ERN/LRPT is administered via an abbreviated, two-step dose advancement regimen: 1 g/20 mg for four weeks followed by 2 g/40 mg for maintenance. The present study evaluated the lipid-altering efficacy and safety (specifically, effects on glycaemic control) of ERN/LRPT versus placebo in a patient population with T2DM.

Methods

Patient selection criteria

Eligible patients included men and women from 18 to 80 years of age with a confirmed diagnosis of T2DM. Patients were required to have LDL-C <2.97 mmol/L and ≥1.55 mmol/L (<115 mg/dL and ≥60 mg/dL) and TG ≤5.65 mmol/L (500 mg/dL) prior to randomisation and be on a stable dose of anti-diabetes mellitus medication (including insulin) for three months prior to visit 1. Patients with type 1 diabetes were excluded from the study. Patients with the following laboratory values at visit 1 were excluded: creatinine >2.0 mg/dL, alanine aminotransferase (ALT) >1.5x upper limit of normal (ULN), aspartate aminotransferase (AST) >1.5x ULN, creatine kinase (CK) >2x ULN, and thyroid stimulating hormone (TSH) >20% above the central laboratory's normal reference range. Patients with poorly controlled (HbA_{1c} >8.5% at visit 1) or newly diagnosed T2DM (within three months of randomisation) were also excluded. Concomitant drugs that were excluded at study entry included niacin ≥50 mg/day, Cholestin (red yeast rice), concomitant use of fibrate with statin, torcetrapib within one year of visit 1, anti-obesity therapy within three months of randomisation, cyclical hormonal contraceptives or intermittent use of hormone replacement therapies, and systemic corticosteroids.

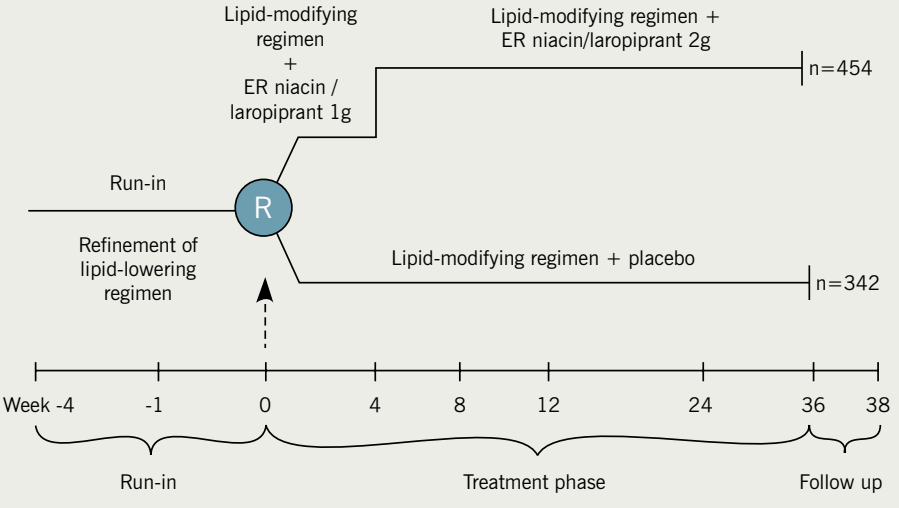
Study design

This was a worldwide, multi-centre, double-blind, randomised, placebo-controlled, parallel-group study (protocol number 069; first patient in on 27 July 2007, last patient/last visit on 1 August 2008), with a 36-week double-blind treatment period, preceded by a four-week lipid-modifying run-in period to attain LDL-C <2.97 mmol/L (115 mg/dL), if necessary (**figure 1**). Detailed information on the patients' antihyperglycaemic regimen was collected at the randomisation visit. Allowable run-in adjustments included increasing the statin dose, switching to a more effective statin, adding ezetimibe or a bile acid sequestrant. If a patient was receiving a statin, the investigator was prohibited from adding a fibrate to the patient's regimen. Eligible patients were randomised in a 4:3 ratio to double-blind treatment, starting with ERN/LRPT 1 g (one tablet of ERN 1 g/LRPT 20 mg) or placebo.

Randomisation of study drug was achieved via an Interactive Voice Response System. After four weeks of treatment, doses were doubled (two tablets), increasing the ERN/LRPT doses to 2 g/40 mg for the remainder of the study. No adjustments to background lipid-modifying regimens were allowed for the first 12 weeks of the study. After 12 weeks, patients with LDL-C >2.84 mmol/L (110 mg/dL) on consecutive measures could have their non-niacin lipid-modifying regimen adjusted to attain LDL-C <2.84 mmol/L (110 mg/dL). There were eight scheduled clinic visits at weeks –4, –1, 0 (day 1), 4, 8, 12, 24 and 36. The final visit was followed two weeks later by a post-study telephone contact to assess potential serious adverse experiences (AEs).

The following laboratory abnormalities were prespecified as values that warranted study discontinuation: consecutive ALT and/or AST elevations ≥3x ULN; consecutive CK elevations ≥5x and <10x ULN with muscle symptoms, consecutive CK elevations ≥10x ULN with or without muscle symptoms, or single CK elevations ≥20x ULN with or without muscle symptoms; consecutive fasting TG >6.77 mmol/L (600 mg/dL); or a positive pregnancy

Figure 1. Study design



test. Study discontinuation was also pre-specified for patients who experienced hypersensitivity or other severe intolerance to study therapy or who required continuous treatment with systemic corticosteroids.

The study protocol was reviewed and approved by the appropriate ethics committees/institutional review boards. All patients provided written informed consent. The study was performed under the guidelines established by the Declaration of Helsinki and Good Clinical Practice standards.

Efficacy assessments

The primary end point was efficacy of ERN/LRPT versus placebo on percentage change from baseline in LDL-C levels from baseline to 12 weeks of active treatment. Additional end points included efficacy of ERN/LRPT versus placebo on percentage change from baseline to 12 weeks in HDL-C, TG, LDL-C/HDL-C ratio, non-HDL-C, apolipoprotein (Apo) B, Apo A-I, TC, TC/HDL-C ratio, Lp(a) and C-reactive protein (CRP) after 12 weeks. Subgroup analyses for the percentage change from baseline in LDL-C from baseline to week 12 were performed to explore the consistency of the treatment effect by age (<65, ≥65 years), gender, race (Caucasian, Asian, other), and being at LDL-C goal ≤2.59 mmol/L (100 mg/dL) at baseline (yes, no).

Safety

Safety was evaluated by reviewing patient-reported AEs, investigators' observations and assessments, and specific laboratory tests. While blinded to study drug, investigators determined the severity of AEs (mild, moderate, severe or life-threatening) and the potential relationship to treatment (definitely not, probably not, possibly, probably, definitely). Key safety variables were the incidence of any clinical or laboratory AEs, treatment-related AEs, serious AEs, and discontinuations due to AEs. Laboratory evaluations included ALT, AST, CK, FPG, HbA_{1c} and other general surveillance labs (haematology, chemistry, urinalysis, beta-human chorionic gonadotropin). The percentage of patients with worsening of T2DM, defined as experiencing a diabetes-related AE and/or requiring an intensification of anti-diabetes mellitus medication, was assessed. The percentage of patients with a change in antihyperglycaemic medication was also assessed and characterised by investigators as increased, decreased or unchanged in intensity. Several factors (baseline HbA_{1c}, glucose, insulin use, gender and body mass index [BMI]) were evaluated for influencing the intensification of antihyperglycaemic medication in a *post hoc* analysis using logistic regression. Serious cardiovascular AEs were adjudicated by an independent expert committee.

Laboratory analyses

Blinded lipid determinations were performed on fasting plasma samples by a central laboratory (PPD Global Central Laboratories, Highland Heights, KY, USA or Zaventem, Belgium) according to standards specified by the National Heart Lung and Blood Institute and Centers for Disease Control and Prevention.[24] LDL-C was calculated using the Friedewald equation.[25] In the event of a TG value >4.52 mmol/L (400 mg/dL), LDL-C was measured by preparative ultracentrifugation (15 minutes at 2,000 rpm) and separation using a Fisherbrand® Ulti-Sep™ Serum Separator (Fisher Scientific, Pittsburgh, PA, USA). Plasma cholesterol and TG were determined using enzymatic methods. HDL-C was measured after precipitation of the Apo B-containing lipoproteins (LDL and very low-density lipoprotein [VLDL]) from whole plasma by heparin-manganese chloride. Non-HDL-C levels were calculated by subtracting HDL-C from TC values. Apo B was quantified by immunonephelometry. Glucose was measured in plasma at screening and throughout the study.

Statistical analysis

The efficacy of ERN/LRPT (1 g → 2 g) relative to placebo at week 12 was assessed using a repeated measures analysis. The model used repeated measurements at three study times (weeks 4, 8 and 12) and had fixed effects for treatment-by-time interaction, gender-by-time interaction and baseline-by-time interaction. Similar repeated measures models were used to analyse percentage change from baseline in HDL-C and other lipid parameters (except TG, CRP and Lp[a]) at week 12. For the percentage change from baseline in LDL-C at week 12, a supportive analysis based on an analysis of covariance (ANCOVA) model including terms for treatment, gender and the baseline lipid value as covariate was performed. A similar sensitivity analysis was provided for the percentage change from baseline at week 12 in other lipid parameters. The comparison of treatment groups in TG, CRP and Lp(a) at week 12 was performed using an ANCOVA model applied to Tukey's normalised ranks of the percentage change from baseline; the model included terms for treatment, gender and Tukey's normal score of the baseline as a covariate.

Safety was assessed by statistical and clinical review of AEs, laboratory values, and vital signs. Inferential comparisons (95% confidence interval [CI] and p values for treatment difference) were provided for the following key safety parameters: hepatitis-related AEs (based on investigator report), ALT and/or AST consecutive elevations ≥3x ULN, CK elevations ≥10x ULN, CK elevations ≥10x ULN with muscle symptoms, CK elevations ≥10x ULN with treatment-related muscle symptoms, confirmed adjudicated cardiovascular AEs and worsening of diabetes, defined as experiencing a diabetes-related AE and/or requiring an intensification of anti-diabetes mellitus medication. Inferential comparisons (95% CI and p values for treatment difference) were also performed for the percentage of patients with a change in antihyperglycaemic medication. For the following AEs, the 95% CI for the treatment difference was provided: overall AEs, overall serious AEs, overall AEs leading to discontinuation, overall treatment-related AEs, AEs by system organ class, and specific AEs that occurred in at least four patients in one or more treatment group. Additional laboratory events of interest included the proportion of patients meeting the predefined limits of change and change from baseline analyses to study end in FPG and HbA_{1c}. Summary statistics over time were calculated for all haematology, blood chemistry and vital sign parameters.

Results

Patients

Overall, 1,404 patients were screened and 796 patients met the inclusion criteria and were randomised (454 patients in the ERN/LRPT group and 342 patients in the placebo group). In total, 221 patients discontinued prior to completion, and 575 patients completed the study (**figure 2**). There were no clinically meaningful differences in baseline demographic, anthropometric, or disease characteristics between the treatment groups (**table 1**). Baseline lipid variables and prior drug therapies were also generally similar across the treatment groups (**table 1**). The vast majority of randomised patients (~90%) were dyslipidaemic based on medical history or baseline lipid levels; approximately 80% were taking statins and 99% were on an antihyperglycaemic regimen.

Figure 2. Consort diagram

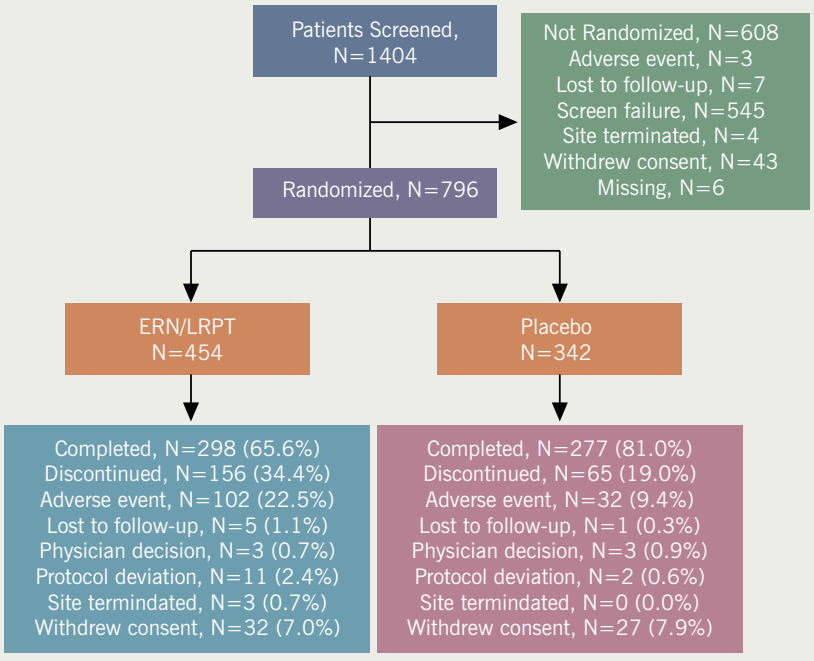
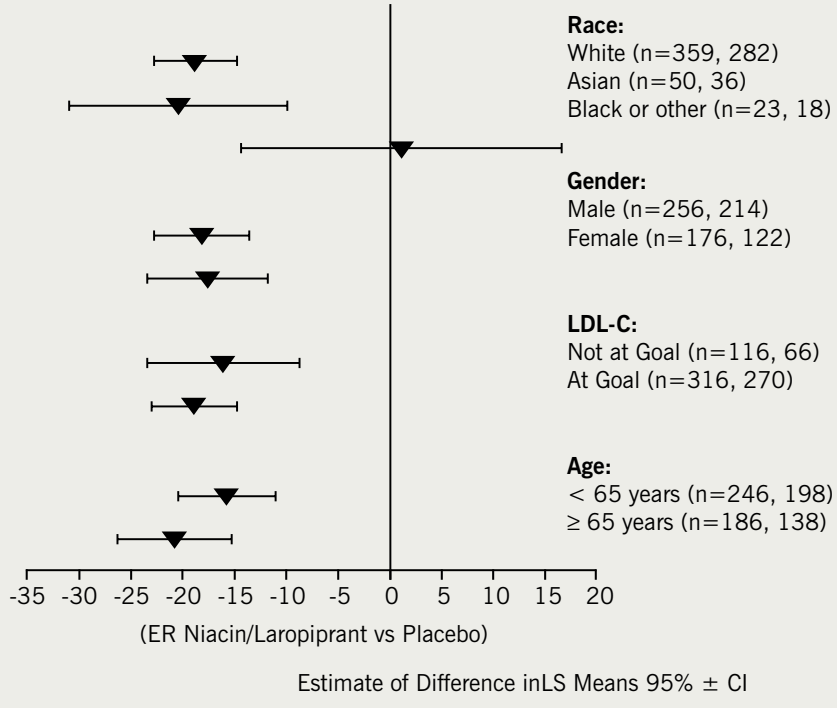


Figure 3. Estimate of treatment difference in percentage change from baseline in low-density lipoprotein cholesterol (LDL-C) at week 12 in subgroups defined by baseline race, gender, LDL-C goal status and age. Least squares mean ± 95% confidence interval (CI) within each level of specific subgroup (full analysis set)



n=x, y, x: patients in ER Niacin/Laropiprant, y: patients in placebo

Efficacy parameters

Significantly ($p \leq 0.001$) greater mean percentage reductions in LDL-C were observed from baseline to week 12 with ERN/LRPT versus placebo (**table 2**). The LDL-C treatment effects were generally consistent across pre-specified subgroups defined by patient baseline characteristics, including age, gender, race, and being at LDL-C goal at baseline (**figure 3**). Treatment effects were also consistent across baseline HDL-C levels (above or below 40 mg/dL [men] or 50 mg/dL [women]) and baseline TG levels (above or below 150 mg/dL) (data not shown).

Significantly greater percentage changes from baseline to week 12 with ERN/LRPT versus placebo were also observed for HDL-C, TG, TC, TC:HDL-C ratio, LDL-C:HDL-C ratio, Apo B, Apo A-I, non-HDL-C, Apo B:Apo A-I ratio, Lp(a) and CRP (**table 2**). The lipid-altering effects of ERN/LRPT were maintained over 36 weeks for the three key lipid parameters (LDL-C, HDL-C and TG; **figure 4**) and for all other efficacy parameters (data not shown). The HDL-C and TG treatment effects were generally consistent across pre-specified subgroups defined by patient baseline characteristics, including age, gender, race, and baseline levels of LDL-C, HDL-C and TG (data not shown).

Safety

Treatment-related AEs and discontinuations due to treatment-related AEs were more common in the ERN/LRPT group (**table 3**). The most common AEs leading to discontinuation in the ERN/LRPT versus placebo groups, respectively, were pruritus (3.6% *vs.* 0%), flushing (2.0% *vs.* 0.9%), diarrhoea (1.8% *vs.* 0.6%), rash (1.8% *vs.* 0.3%), vomiting (1.1% *vs.* 0%) and FPG increased (2.2% *vs.* 0%).

There was only one hepatitis-related AE, which occurred in the placebo group. Consecutive ≥3x ULN elevations in ALT and/or AST were seen in three (0.7%) and one (0.3%) patient(s) in the ERN/LRPT and placebo groups, respectively ($p=0.6$; **table 3**). All ALT/AST elevations were asymptomatic and resolved with discontinuation of treatment. No subject experienced myopathy or rhabdomyolysis or CK elevations ≥10x ULN (**table 3**). The incidence of confirmed adjudicated cardiovascular AEs was similarly low in both treatment arms (**table 3**).

Mild increases in FPG and HbA_{1c} were observed in both treatment arms, however, a greater increase was seen in FPG (**table 4**, **figures 5 and 6**). The increases in FPG peaked by eight weeks and gradually declined thereafter (**figure 5**). Slightly

Table 1. Demographics and baseline characteristics

Parameter*	ERN/LRPT (n=454)	Placebo (n=342)
Demographic parameters		
Age (years) mean ± SD	62 ± 9.3	62 ± 9.4
Gender, n (%)		
Females	188 (41.4)	126 (36.8)
Males	266 (58.6)	216 (63.2)
Race, n (%)		
White	378 (83.3)	286 (83.6)
Black	15 (3.3)	11 (3.2)
Asian	50 (11.0)	36 (10.5)
Other	11 (2.4)	9 (2.6)
BMI (kg/m^2) mean ± SD	31.2 ± 6.5	30.5 ± 5.8
Efficacy parameters		
LDL-C (mmol/L) mean ± SD	2.2 ± 0.5	2.2 ± 0.5
HDL-C (mmol/L) mean ± SD	1.3 ± 0.3	1.3 ± 0.3
TG (mmol/L) median	1.4	1.5
LDL-C:HDL-C ± SD	1.9 ± 0.6	1.8 ± 0.5
Apo B (g/L) ± SD	0.9 ± 0.2	0.9 ± 0.2
Apo A-1 (g/L) ± SD	1.5 ± 0.3	1.5 ± 0.3
TC (mmol/L) ± SD	4.3 ± 0.7	4.2 ± 0.6
TC:HDL-C ± SD	3.5 ± 1.0	3.4 ± 0.8
Non-HDL-C (mmol/L) ± SD	3.0 ± 0.6	2.9 ± 0.6
Lp(a) (g/L) median	0.1	0.1
CRP (mg/L) median	1.9	1.5
Glycaemic parameters		
FPG (mmol/L) mean ± SD	7.3 ± 1.9	7.4 ± 1.8
HbA_{1c} mean ± SD	6.9 ± 0.7	6.9 ± 0.7
Prior therapy*		
Antihyperglycaemic therapy, n (%)		
Insulin	88 (19.4)	66 (19.3)
Biguanide	344 (75.8)	252 (73.7)
Thiazolidinediones	72 (15.9)	44 (12.9)
Sulphonylureas	149 (32.8)	114 (33.3)
Other	64 (14.1)	53 (15.5)
Naive	5 (1.1)	4 (1.2)
Lipid-modifying therapy, n (%)		
Statin	349 (76.9)	271 (79.2)
Other	44 (9.7)	36 (10.5)
Naive	83 (18.3)	60 (17.5)

Key: Apo = apolipoprotein; BMI = body mass index; CRP = C-reactive protein; ERN = extended-release niacin; FPG = fasting plasma glucose; HbA_{1c} = glycosylated haemoglobin; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp = lipoprotein; LRPT = laropiprant; SD = standard deviation; TC = total cholesterol; TG = triglycerides

*Participants could be categorised in more than one class of prior therapy. Medication intakes that stopped more than one month prior to randomisation are not considered for the prior antihyperglycaemic/lipid-modifying therapy classification

Table 2. Least squares mean percentage change† (95% confidence interval [CI]) from baseline to week 12 in efficacy parameters among patients treated with extended-release niacin (ERN)/laropiprant (LRPT) 2 g/40 mg versus placebo

Efficacy parameters	ERN/LRPT n=432‡	Placebo n=336‡	Between-treatment group difference in percentage change from baseline (95% CI)
LDL-C	–15.8 (–18.4, –13.2)	2.1 (–0.3, 4.6)	–17.9 (–21.4, –14.4)**
HDL-C	25.4 (23.4, 27.5)	2.2 (0.6, 3.8)	23.2 (20.7, 25.7)**
TG (median)	–22.2 (–25.5, –18.8)	2.3 (–1.6, 6.2)	–23.1 (–27.2, –18.9)**
LDL-C/HDL-C ratio	–30.8 (–33.4, –28.2)	1.2 (–1.4, 3.7)	–32.0 (–35.5, –28.4)**
Non-HDL-C	–17.6 (–19.8, –15.5)	2.2 (0.0, 4.3)	–19.8 (–22.8, –16.8)**
Apo B	–14.5 (–16.3, –12.7)	2.6 (0.6, 4.6)	–17.1 (–19.7, –14.5)**
Apo A-I	9.3 (8.0, 10.6)	1.1 (–0.4, 2.6)	8.2 (6.3, 10.2)**
TC	–4.4 (–5.8, –2.9)	2.1 (0.5, 3.7)	–6.5 (–8.6, –4.4)**
TC/HDL-C ratio	–21.9 (–23.8, –20.1)	1.0 (–0.8, 2.8)	–22.9 (–25.4, –20.4)**
Lp(a) (median)	–25.0 (–29.0, –21.0)	0.0 (–2.8, 2.8)	–25.0 (–28.6, –20.2)**
CRP (median)	0.0 (–7.9, 7.9)	14.3 (6.4, 22.2)	–16.9 (–26.4, –7.7)*

Key: Apo = apolipoprotein; CRP = C-reactive protein; FPG = fasting plasma glucose; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; Lp = lipoprotein; TC = total cholesterol; TG=triglycerides

†Unless otherwise stated

‡Sample size is based on the number of patients included in the analysis of the primary lipid end point (percentage change from baseline at week 12 in LDL-C)

** p≤0.001
* p=0.004

Table 3. Summary of adverse experiences (AE) after 36 weeks of treatment, all patients as treated

Parameter	ERN/LRPT n/N (%)	Placebo n/N (%)	Between-treatment difference (95% CI)
Treatment-related clinical AE†	229/449 (51.0)	99/340 (29.1)	21.9 (15.1, 28.4)
Treatment-related laboratory AE†	68/449 (15.1)	25/340 (7.4)	7.8 (3.3, 12.1)
Discontinued due to treatment-related clinical AE†	79/449 (17.6)	23/340 (6.8)	10.8 (6.3, 15.2)
Discontinued due to treatment-related laboratory AE†	14/449 (3.1)	1/340 (0.3)	2.8 (1.0, 4.9)
Liver effects			
Hepatitis-related clinical AE*	0/449 (0.0)	1/340 (0.3)	–0.3 (–1.6, 0.6)
Consecutive or presumed consecutive ALT and/or AST elevations ≥3x ULN	3/434 (0.7)	1/337 (0.3)	0.4 (–1.0, 1.7)
Muscle effects			
Myopathy**	0/434 (0.0)	0/337 (0.0)	0.0 (–1.1, 0.9)
CK elevations ≥10x ULN	0/434 (0.0)	0/337 (0.0)	0.0 (–1.1, 0.9)
Cardiovascular effects			
Confirmed adjudicated cardiovascular events	1/449 (0.2)	4/340 (1.2)	–1.0 (–2.8, 0.3)

Key: ALT = alanine aminotransferease; AST = aspartate aminotransferase; CI = confidence interval; CK = creatine kinase; ERN = extended-release niacin; LRPT = laropiprant; ULN = upper limit of normal

†Determined by the investigator to be possibly, probably or definitely treatment-related

*Identified by a collective review using the following pre-specified set of terms: cholestasis, hepatic necrosis, hepatocellular damage, cytolytic hepatitis, hepatitis, hepatomegaly, jaundice, hepatic failure, hepatitis cholestatic, jaundice cholestatic, hepatitis fulminant, hyperbilirubinaemia, jaundice hepatocellular, ocular icterus, yellow skin, hepatic function abnormal, acute hepatic failure, subacute hepatic failure, hepatitis acute, hepatitis toxic, hepatotoxicity, and mixed hepatocellular-cholestatic injury

Presumed consecutive = subjects with two consecutive measurements for ALT and/or AST ≥3× ULN and a single, last measurement ≥3× ULN or a measurement ≥3× ULN followed by a measurement <3× ULN that was taken more than 2 days after the last dose of study medication

**Increases in CK to ≥10x ULN accompanied by unexplained muscle symptoms

Table 4. Summary of glucose-related adverse experiences (AEs)

Parameter	ERN/LRPT	Placebo	Between-treatment difference (95% CI)
FPG (mmol/L)			
Laboratory AE of FPG increased, n/N (%)	52/449 (11.6)	14/340 (4.1)	7.5 (3.7, 11.1)
LS mean change in FPG	0.5 (7.3 → 7.9)	0.2 (7.4 →7 .6)	0.4 (0.06, 0.67)
Median change in FPG	0.4 (7.1 → 7.5)	0.1 (7.2 → 7.2)	0.3 (0.06, 0.5)
HbA_{1c} (%)			
Laboratory AE of HbA_{1c} increased, n/N (%)	12/449 (2.7)	2/340 (0.6)	2.1 (0.2, 4.1)
LS mean change in HbA_{1c}	0.34 (6.9 → 7.3)	0.16 (6.9 → 7.1)	0.18 (0.08, 0.28)
Median change in HbA_{1c}	0.30 (6.8 → 7.2)	0.20 (6.8 → 7.0)	0.10 (0.00, 0.20)
Worsening of diabetes	89/449 (19.8)	36/340 (10.6)	9.2 (4.2, 14.1)*
Based on clinical AE of diabetes mellitus only	10/449 (2.2)	8/340 (2.4)	–0.1 (–2.6, 2.0)
Based on intensification of antihyperglycaemic medication only	72/449 (16.0)	24/340 (7.1)	9.0 (4.6, 13.4)
Based on both	7/449 (1.6)	4/340 (1.2)	0.4 (–1.6, 2.2)
Overall intensification of antihyperglycaemic medication	79/449 (17.6)	28/340 (8.2)	9.3 (4.7, 14.0)*

Key: CI = confidence interval; ERN = extended-release niacin; FPG = fasting plasma glucose; HbA_{1c} = glycosylated haemoglobin; LRPT = laropiprant; LS = least squares

*p≤0.001

greater increases in FPG and HbA_{1c} were observed in the subgroup of patients with an intensification in antihyperglycaemic medication regimen (**figures 5 and 6**); these subgroup plots should be interpreted with caution because the subgroups were determined by a post-randomisation outcome (intensification in antihyperglycaemic medication regimen). Overall, 3.3% of patients in the ERN/LRPT group discontinued due to a glucose or diabetes-related AE compared with 0.3% in the placebo group (diabetes mellitus: 0.2% *vs.* 0.3%; hyperglycaemia: 0.7% *vs.* 0%; blood glucose increased: 2.2% *vs.* 0%; HbA_{1c} increased: 0.2% *vs.* 0%, respectively).

A higher proportion of patients in the ERN/LRPT group (17.6%) compared with the placebo group (8.2%) had an overall intensification in antihyperglycaemic medication regimen during the nine-month treatment period (odds ratio [95% CI]: 2.38 [1.51, 3.76]; p<0.001). In a univariate analysis, baseline HbA_{1c}, glucose, insulin use and gender were also strong predictors of intensification of antihyperglycaemic medication, regardless of treatment; BMI was not significant (**table 5**). There was no interaction between these predictors and treatment. After applying a stepwise regression on the logistic model, baseline HbA_{1c} (p<0.001), treatment (p<0.001) and gender (p=0.019) remained significant. Finally, the types of medication adjustments were qualitatively similar between the ERN/LRPT and placebo groups, with no meaningful differences regarding the proportion of patients requiring dose increases only (65% and 50%, respectively), addition of a medication only (11% and 18%) or both (24% and 32%). Overall, only two (2.5%) patients in the ERN/LRPT group and one (3.6%) patient in the placebo group required the addition of insulin.

Table 5. Factors evaluated for influencing the intensification of antihyperglycaemic medication (AHM) among extended-release niacin (ERN)/laropiprant (LRPT) and placebo-treated patients with type 2 diabetes

Parameter	Group	Intensification of AHM cases/total (%)	Odds ratio	95% CI	p-value†
Baseline HbA_{1c} (%)	Above median (>6.8) Below median (≤6.8)	82/387 (21.2) 25/398 (6.3)	4.01	(2.50, 6.43)	<0.001
Baseline glucose (mg/dL)	Above median (>129) Below median (≤129)	78/388 (20.1) 29/397 (7.3)	3.19	(2.03, 5.02)	<0.001
Insulin user at baseline	Yes No	31/154 (20.1) 76/635 (12.0)	1.85	(1.17, 2.94)	0.009
Gender	Female Male	55/311 (17.7) 52/478 (10.9)	1.76	(1.17, 2.65)	0.007
BMI	Below median (≤29.6) Above median (>29.6)	54/393 (13.7) 53/392 (13.5)	1.02	(0.68, 1.53)	0.928

Key: BMI = body mass index; CI = confidence interval; HbA_{1c} = glycosylated haemoglobin
†Logistic regression with parameter included in model

Discussion

Niacin is an important therapy for patients with T2DM because of its broad lipid-modifying effects. Lowering LDL-C levels has been regarded as the primary lipid-modifying intervention in patients, since several clinical trials have shown an associated reduction in the risk of CVD events in high-risk patients, including those with T2DM.[26-30] The majority of patients in the present study were on a statin and were at or below LDL-C goal at baseline (mean value =2.23 mmol/L [86.3 mg/dL]); however, an LDL-C threshold below which further reduction yields no additional clinical benefit has not been identified. The Heart Protection Study demonstrated significant and similar CVD risk reductions, irrespective of initial LDL-C level, including patients below LDL-C goal.[27] Patients with T2DM remain at high risk for cardiovascular events, despite even intensive LDL-C management to current targets, underscoring the need for addressing additional CVD risk factors.

In epidemiological studies, low HDL-C levels are as strong a predictor of CHD events as elevated LDL-C.[31,32] Results from the Treating to New Targets (TNT) study indicate an association between low levels of HDL-C and elevated CVD risk, even among statin-treated patients with well-controlled LDL-C <1.81 mmol/L (70 mg/dL).[33] Dyslipidaemia in patients with T2DM is often characterised by hypertriglyceridaemia, low HDL-C, an accumulation of cholesterol-rich remnant particles, and a preponderance of small, dense LDL particles.[3,8]

Current recommendations advise the correction of low HDL-C and high TG levels among high-risk patients, including those with T2DM.[1,3,5] ERN/LRPT produces significant improvements across the lipid profile,[34] making it a favourable therapeutic option for T2DM patients with mixed dyslipidaemia. Importantly, the Coronary Drug Project (CDP) and the HDL-Atherosclerosis Treatment Study (HATS) both found that treatment with niacin reduced cardiovascular events in subgroups of patients with T2DM or impaired fasting glucose.[35-37]

In the present study, we found that ERN/LRPT had excellent lipid-modifying efficacy and a favourable safety profile (specifically, effects on glycaemic control) among patients with T2DM. In general, treatment effects on LDL-C, HDL-C and TG between the treatment groups were consistent across all patient subgroups examined. These results were similar to those observed in a previous study that also had a placebo-controlled, add-on design.[34] Favourable lipid-modifying effects with ERN/LRPT compared with placebo were also noted for additional parameters, including significant increases in plasma Apo A-1 and significant decreases in TC, TC:HDL-C ratio, LDL-C:HDL-C ratio, Apo B, non-HDL-C, ApoB:ApoA-1 ratio and Lp(a). Non-HDL-C and Apo B have been identified as predictors of CVD.[38,39]

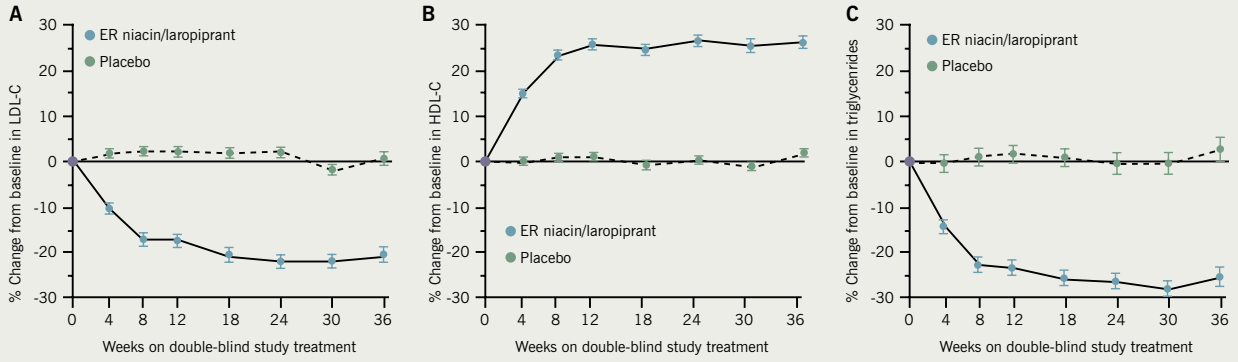
In addition to lipid/lipoprotein parameters, an inflammation process may be important in atherosclerosis and thrombosis. The inflammatory marker, CRP, is a predictor of CHD-related morbidity and mortality, independent of traditional risk factors.[40-43] The literature is mixed on the effect of niacin on CRP, with reductions observed in some studies but not others.[44-48] In the present study, there was a significant difference in median percentage change in CRP: 0.0% in the ERN/LRPT group versus 14.3% in the placebo group (p=0.004).

Adverse events

ERN/LRPT had an AE profile similar to that observed in prior studies with ERN/LRPT.[34] AEs that were treatment related or led to discontinuation occurred more frequently in the ERN/LRPT group than in the placebo group. The AEs reported more frequently in the ERN/LRPT group were non-serious side effects, typically associated with niacin or niacin-containing products; specifically, clinical AEs related to flushing, pruritus, rash, and gastrointestinal symptoms and laboratory AEs related to elevations in FPG. The only hepatitis-related AE was in the placebo group. The incidence of consecutive elevations ≥3x ULN in ALT and/or AST, which were all asymptomatic and resolved with treatment cessation, is consistent with results from previous studies.[34] No subject had myopathy or rhabdomyolysis and no clinically meaningful increases in CK (≥10x ULN).

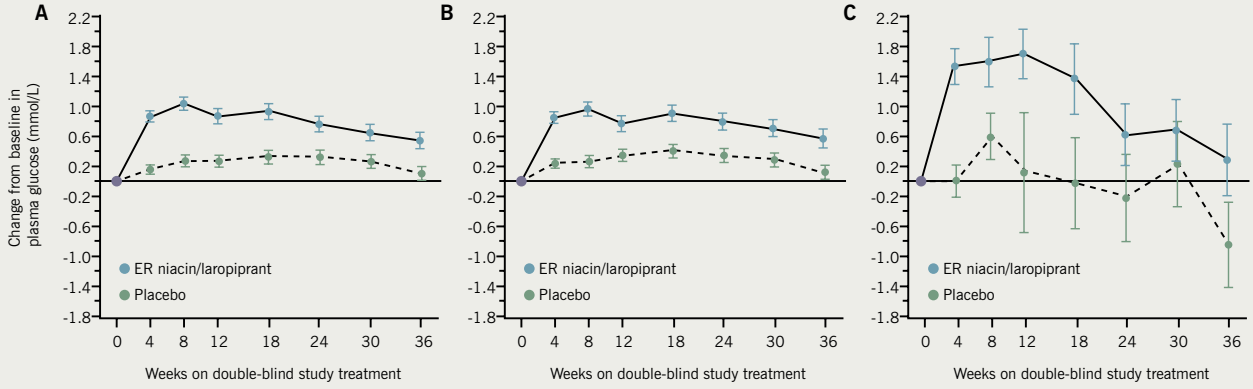
Niacin may contribute to insulin resistance and raise FPG levels and was, therefore, considered relatively contraindicated in patients with T2DM.[1] However, this belief is based on early research that showed a high incidence of hyperglycaemia and discontinuation with immediate-release niacin at higher doses (1.5 g three times daily).[49]

Figure 4. Percentage change from baseline to week 36 in (A) low-density lipoprotein cholesterol (LDL-C); (B) high-density lipoprotein cholesterol (HDL-C); and (C) triglycerides (TG). Data are shown as treatment group mean (± SE) percentage change from baseline for HDL-C and LDL-C, and treatment group median (± SE) percentage change from baseline for TG (full analysis set)



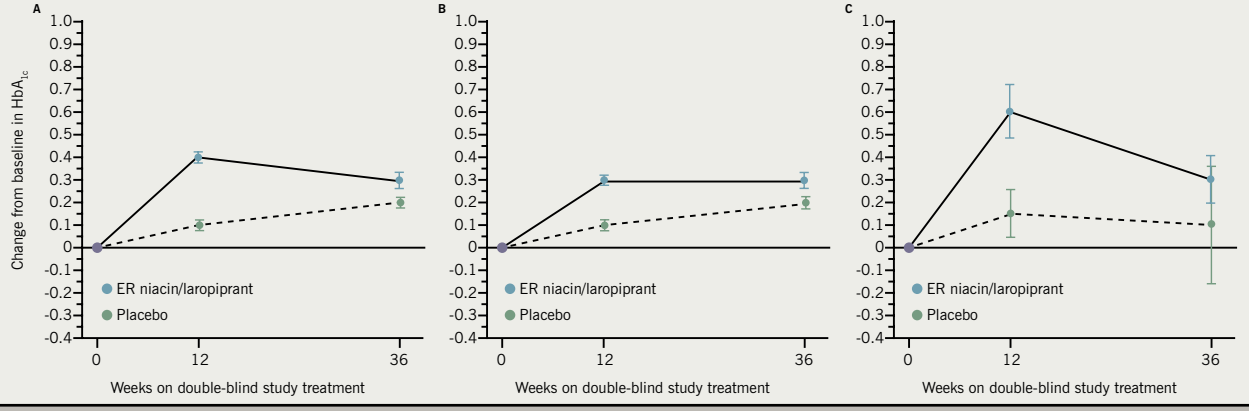
Key: ER = extended-release

Figure 5. Median change (± SE) from baseline to week 36 in fasting plasma glucose (mmol/L) (all patients as treated) in the entire study cohort (A), patients without an intensification in antihyperglycaemic medications (B), and patients with an intensification in antihyperglycaemic medications (C)



Key: ER = extended-release

Figure 6. Median change (± SE) from baseline to week 36 in glycosylated haemoglobin (HbA_{1c}, %) (all patients as treated) in the entire study cohort (A), patients without an intensification in antihyperglycaemic medications (B), and patients with an intensification in antihyperglycaemic medications (C)



Key: ER = extended-release

In the present study, one of the largest studies of extended-release niacin in patients with T2DM, ERN/LRPT produced modest changes in FPG, which were managed with adjustments in the antihyperglycaemic regimen in a subset of patients. These findings are entirely consistent with smaller studies, showing that ERN (1 g or 1.5 g daily) in patients with T2DM produced slight, transient increases in FPG and a low discontinuation rate.[50] In addition, HbA_{1c} did not change significantly in the ERN 1 g or placebo groups, and increased by 0.29% (p=0.048) in the ERN 1.5 g/day group. Although adjustments in antidiabetic medications were permitted,[50] these changes did not differ significantly between study arms. Similar findings of modest, transient increases in glucose and non-significant increases in antidiabetic regimens were noted with niacin in another clinical trial. In light of these data, current guidelines for the treatment of dyslipidaemia in T2DM list niacin as a valid treatment option.[51]

A pre-specified objective of this study was to assess the proportion of patients requiring intensification of their antihyperglycaemic regimen. For this reason, adjustments in antihyperglycaemic therapy were recorded and investigators were asked to assess whether or not patients experienced an overall net intensification in therapy over the course of the study. In the ERN/LRPT group, 17.6% of patients had an overall intensification in antihyperglycaemic medication regimen versus 8.2% of patients in the placebo group over the nine-month treatment period. A similar trend was observed in the Arterial Disease Multiple Intervention Trial (ADMIT) study, in which 29% of patients with diabetes mellitus taking 1.5 g of Niaspan™ increased dosage or added a new drug to their anti-diabetes mellitus regimen versus 16% of patients taking placebo over 16 weeks of treatment.[50] In the present study, more patients treated with ERN/LRPT versus placebo required intensification of antihyperglycaemic medications over nine months. The predictors of antihyperglycaemic medication adjustment, as well as the overall types of adjustments required to manage glycaemic status, were similar in both treatment groups.

Conclusion

This study demonstrated that in patients with T2DM, treatment with ERN/LRPT (with or without other stable lipid-modifying therapy) produced superior lipid-altering efficacy at week 12 relative to placebo across the entire lipid profile, including the three major lipid parameters linked with CVD. Additionally, ERN/LRPT in patients with T2DM had a safety profile consistent with ERN/LRPT and with ERN alone in other patient populations.[34] This 36-week study suggests that the glucose-elevating effects of ERN/LRPT in patients with T2DM were manageable for the majority of patients. ERN/LRPT may be an important addition to the clinicians' armamentarium for the management of dyslipidaemia in patients with T2DM, a population with the highest risk for cardiovascular events

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Conflict of interest

Y Mitchel, H Giezek, K Vandormael, R Ruck, K Gibson, C McCrary Sisk and D Maccubbin are employees of Merck & Co., Inc. and may hold stock/stock options in the company. J McKenney, R Scott, E Brinton and H Bays have received consultant/speaker honoraria and/or research grants from Merck & Co., Inc. A MacLean and J Paolini are former employees of Merck & Co., Inc. and may hold stock in the company.

Key messages

- We evaluated the lipid-altering efficacy and safety (especially, glycaemic control) of extended-release niacin/laropiprant (ERN/LRPT; a tablet containing 1 g ERN and 20 mg LRPT) in patients with type 2 diabetes mellitus (T2DM)
- At week 12, ERN/LRPT produced significant (p≤0.001 for all) percentage changes from baseline in low-density lipoprotein cholesterol (LDL-C) (–17.9%), high-density lipoprotein cholesterol (HDL-C) (23.2%), LDL-C:HDL-C (–32.0%), triglycerides (–23.1%), apolipoprotein (Apo) B (–17.1%), Apo A-I (8.2%) and total cholesterol (TC):HDL-C (–22.9%) versus placebo
- From baseline to week 36, median fasting plasma glucose (FPG) and glycosylated haemoglobin (HbA_{1c}) increased with ERN/LRPT from 7.31 to 7.88 mmol/L and 6.9 to 7.3%, respectively, consistent with known niacin effects
- In this population of patients with T2DM, ERN/LRPT produced significant, durable improvements in lipids/lipoproteins and had a safety profile consistent with ERN/LRPT and ERN alone in other populations

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