Journal of Clinical Lipidology (2015) 9, 313–325

Journal of Clinical Lipidology

Safety and tolerability of extended-release niacin-laropiprant: Pooled analyses for 11,310 patients in 12 controlled clinical trials

James McKenney, PharmD, Harold Bays, MD, Gilbert Gleim, PhD, Yale Mitchel, MD*, Olga Kuznetsova, PhD, Aditi Sapre, PhD, Waheeda Sirah, MS, Darbie Maccubbin, PhD

Virginia Commonwealth University School of Pharmacy, Richmond, VA, USA (Dr McKenney); Louisville Metabolic and Atherosclerosis Research Center, Louisville, KY, USA (Dr Bays); Clinical Research, Merck & Co, Inc, Kenilworth, NJ, USA (Drs Gleim, Mitchel, Maccubbin and Ms Sirah); and Late Development Statistics, Merck & Co, Inc, Kenilworth, NJ, USA (Drs Kuznetsova and Sapre)

KEYWORDS:
Extended-release niacin;
Laropiprant;
Safety;
Pooled analysis;
Clinical trials

BACKGROUND: The Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events (HPS2-THRIVE) showed that adding extended-release niacin-laropiprant (ERN-LRPT) to statin provided no incremental cardiovascular benefit vs placebo (PBO). ERN-LRPT was also associated with an excess of serious adverse experiences (AEs), some of which were unexpected (infections and bleeding). These findings led to the withdrawal of ERN-LRPT from all markets.

OBJECTIVE: We examined the safety profile of ERN-LRPT vs the comparators ERN alone and statins in the ERN-LRPT development program to assess whether similar safety signals were observed to those seen in HPS-THRIVE and whether these might be attributed to ERN or LRPT.

METHODS: Postrandomization safety data from 12 clinical studies, 12 to 52 weeks in duration and involving 11,310 patients, were analyzed across 3 treatments: (1) ERN-LRPT; (2) ERN-NSP (ERN, Merck & Co, Inc or Niaspan [NSP], Abbott Laboratories); and (3) statin-PBO (statin or PBO).

RESULTS: The safety profiles of ERN-LRPT and ERN-NSP were similar, except for less flushing with ERN-LRPT. Nonflushing AEs reported more frequently with ERN-LRPT or ERN-NSP than with statin-PBO were mostly nonserious and typical of niacin (nausea, diarrhea, and increased blood glucose). There was no evidence for an increased risk of serious AEs related to diabetes, muscle, infection, or bleeding.

CONCLUSIONS: Pooled data from 11,310 patients revealed that, except for reduced flushing, the safety profile of ERN-LRPT was similar to that of ERN-NSP; LRPT did not appear to adversely affect the side-effect profile of ERN. The inability to replicate the unexpected AE findings in HPS2-THRIVE could be because of the smaller sample size and substantially shorter duration of these studies.

Introduction

Extended-release niacin-laropiprant (ERN-LRPT; Merck & Co, Inc) is a fixed-dose combination product containing a Merck-developed ERN and LRPT, an agent, which reduces niacin-induced flushing[1,2] by selectively blocking the prostaglandin D_2 receptor-1 in the skin.[3] The

These studies were supported by Merck & Co., Inc., Kenilworth, New Jersey, USA.

* Corresponding author. Merck & Co, Inc, P.O. Box 2000, RY34-A228, Rahway, NJ 07065.
E-mail address: yale_mitchel@merck.com

Submitted August 8, 2014. Accepted for publication February 25, 2015.

1933-2874/
http://dx.doi.org/10.1016/j.jacl.2015.02.006

efficacy of ERN-LRPT to raise blood levels of high-density lipoprotein (HDL) cholesterol and to lower low-density lipoprotein (LDL) cholesterol (LDL-C) and triglycerides was shown to be similar to other forms of ERN at equivalent doses.[2,4] Furthermore, except for significantly less niacin-induced flushing with ERN-LRPT, the safety profile of ERN-LRPT appeared to be similar to comparable doses of ERN and other ERN formulations.[2,4,5] Based on these findings, ERN-LRPT was first approved in 2008 in the European Union and a number of other countries for the treatment of dyslipidemia.

The results of numerous small imaging studies have shown that niacin (immediate- and extended-release forms) slows progression or promotes regression of atherosclerotic lesions.[6–10] Furthermore, the Coronary Drug Project (conducted before the availability of statins) provided evidence that the LDL cholesterol–lowering and HDL cholesterol–raising effects of niacin monotherapy were associated with a reduced risk of death and cardiovascular events relative to placebo (PBO).[11,12]

Statins subsequently became the drug of choice for treatment of elevated LDL cholesterol levels based on their demonstrated lipid efficacy and beneficial effects on cardiovascular outcomes. Thus, it was important to assess the cardiovascular benefits and safety of niacin administered with statins. These were assessed in 2 studies: AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health) and HPS2-THRIVE (Heart Protection Study 2–Treatment of HDL to Reduce the Incidence of Vascular Events).[13,14] In AIM-HIGH, 3414 patients with cardiovascular disease and with low HDL cholesterol (<40 mg/dL [men]; <50 mg/dL [women]), high triglycerides (150–400 mg/dL) and LDL cholesterol optimized to 40 to 80 mg/dL with simvastatin ± ezetimibe, had Niaspan (NSP) of 1.5 to 2 g (Abbott Laboratories), or PBO added to their statin regimen for a median follow-up of 3 years. In HPS2-THRIVE, 25,673 high-risk patients with occlusive vascular disease whose total cholesterol levels had been optimized to <135 mg/dL with simvastatin 40 mg ± ezetimibe, received ERN-LRPT 2 g or PBO for a median follow-up of approximately 4 years. The primary objective in both studies was to determine whether high-dose ERN (as NSP 1.5–2 g or ERN-LRPT 2 g, respectively) would provide incremental cardiovascular benefit beyond that of statin alone. AIM-HIGH was stopped early because of the lack of efficacy,[13] and HPS2-THRIVE failed to achieve statistical significance for the primary end point.[14] Furthermore, among ERN-LRPT–treated patients in HPS2-THRIVE, an excess of multiple body system serious adverse experiences (AEs) was reported; some of these AEs were related to known side effects of niacin (diabetes, musculoskeletal, gastrointestinal, and skin) and others were unexpected (infections and bleeding). Given the lack of cardiovascular efficacy relative to PBO combined with the safety findings in HPS2-THRIVE, ERN-LRPT was withdrawn from all markets globally.[15]

The ERN-LRPT development program included studies in which the efficacy and safety of ERN-LRPT relative to comparators other than PBO, including ERN alone and various statins, were assessed in a large number of patients. In this article, we report the safety findings captured from 11,310 patients (5782 on ERN-LRPT) who participated in 1 of 12 controlled clinical trials ranging in duration from 12 to 52 weeks that were a part of the ERN-LRPT development program. These pooled safety analyses focus primarily on predefined safety parameters related to known side effects of niacin but also examine the unexpected safety findings in HPS2-THRIVE related to infection and bleeding.

Methods

Study designs and populations

Safety data from 9 controlled clinical studies (phase III–V) and 3 phase II, long-term extension studies were pooled (Table 1). Postrandomization safety data from studies in which patients received ERN-LRPT vs a relevant comparator (ERN, PBO, or statin) for at least an 8-week treatment period were eligible for inclusion into the safety pool. Data collected following a switch in treatment were excluded because of potential confounding.

Safety parameters were compared across 3 treatment groups (Table 1):

1. ERN-LRPT: patients randomized to ERN-LRPT across all 12 studies, irrespective of other background lipid-modifying therapies;
2. ERN-NSP: patients randomized to ERN alone (Merck & Co, Inc, Kenilworth, NJ) in P020 or NSP alone in P054, irrespective of other lipid-modifying therapies; and
3. Statin-PBO: patients randomized to a statin or PBO in 11 of the 12 studies. As with ERN-LRPT and ERN-NSP, patients taking PBO may have been on background lipid-modifying therapies, including statins.

Pooling of data from ERN- and NSP-treated patients was considered appropriate because the ERN formulation that was combined with LRPT was selected based on its similarity to NSP with regard to excipients, pharmacokinetic profile, pharmaceutical properties, flushing profile (intrinsic flushing and response to LRPT), lipid-modifying efficacy, and safety or tolerability. This was important because the early LRPT dose-ranging studies and validation of the flushing symptom questionnaire were done using NSP.[16,17]

No group was treated with LRPT alone; therefore, observations about LRPT safety are inferred by examining AEs in patients receiving the combination (ERN-LRPT) vs ERN alone. Concomitant use of low-dose aspirin (81–100 mg) was permitted in all studies; however, higher doses of aspirin, which might mitigate flushing symptoms in patients taking ERN or NSP without LRPT, were excluded