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Impact of concomitant low-dose aspirin on the safety and tolerability of naproxen and esomeprazole magnesium delayed-release tablets in patients requiring chronic nonsteroidal anti-inflammatory drug therapy: an analysis from 5 Phase III studies

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Abstract Patients receiving chronic nonsteroidal anti-inflammatory drugs (NSAIDs) and concomitant low-dose aspirin (LDA) are at increased risk of gastrointestinal (GI) toxicity. A fixed-dose combination of enteric-coated (EC) naproxen and immediate-release esomeprazole magnesium (NAP/ESO) has been designed to deliver a proton-pump inhibitor followed by an NSAID in a single tablet. To examine safety data from 5 Phase III studies of NAP/ESO in LDA users (≤325 mg daily, administered at any time during the study), and LDA non-users, data were analyzed from 6-month studies assessing NAP/ESO versus EC naproxen in patients with osteoarthritis, rheumatoid arthritis, or ankylosing spondylitis ($n = 2$), 3-month studies assessing NAP/ESO vs celecoxib or placebo in patients with knee osteoarthritis ($n = 2$), and a 12-month, open-label, safety study of NAP/ESO ($n = 1$). In an analysis of two studies, incidences of endoscopically confirmed gastric ulcers (GUs) and duodenal ulcers (DUs) were summarized by LDA subgroups. In the pooled analysis from all five studies, incidences of treatment-emergent adverse events (AEs) (including prespecified NSAID-associated upper GI AEs and cardiovascular AEs), serious AEs, and AE-related discontinuations were stratified by LDA subgroups. Overall, 2,317 patients received treatment; 1,157 patients received NAP/ESO and, of these, 298 received LDA. The cumulative incidence of GUs and DUs in the two studies with 6-month follow-up was lower for NAP/ESO vs EC naproxen in both LDA subgroups [GUs: 3.0 vs 27.9 %, respectively, for LDA users, 6.4 vs 22.4 %, respectively, for LDA non-users (both $P < 0.001$); DUs: 1.0 vs 5.8 % for LDA users, 0.6 vs 5.3 % for LDA non-users]. The incidence of erosive gastritis was lower in NAP/ESO- vs EC naproxen-treated patients for both LDA users [18.2 vs 36.5 %, respectively ($P = 0.004$)] and LDA non-users [19.8 vs 38.5 %, respectively ($P < 0.001$)]. Among LDA users, incidences of NSAID-associated upper GI AEs were: NAP/ESO, 16.1 %; EC naproxen, 31.7 %; celecoxib, 22.1 %; placebo, 23.2 %. Among LDA non-users, incidences of NSAID-associated upper GI AEs were: NAP/ESO, 20.3 %; EC naproxen, 36.6 %; celecoxib, 18.5 %; placebo, 18.9 %. For LDA users, incidences of cardiovascular AEs were: NAP/ESO, 3.0 %; EC naproxen, 1.0 %; celecoxib, 0 %; placebo, 0 %. For LDA non-users, incidences of cardiovascular AEs were: NAP/ESO, 1.0 %; EC naproxen, 0.6 %; celecoxib, 0.3 %; placebo, 0 %. NAP/ESO appears to be well-tolerated in patients receiving concomitant LDA. For LDA users, AE incidence was less than that observed for EC naproxen. For most AE categories, incidences were similar among NAP/ESO, celecoxib and placebo groups. The safety of NAP/ESO appeared similar regardless of LDA use.

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Introduction

Nonsteroidal anti-inflammatory drugs (NSAIDs) are commonly used for managing the symptoms of many inflammatory conditions, including osteoarthritis (OA), rheumatoid arthritis (RA), and other arthritic conditions. However, chronic NSAID therapy is associated with an increased risk of adverse gastrointestinal (GI) and cardiovascular (CV) effects. For instance, chronic NSAID users develop endoscopic gastric ulcers (GUs) with point prevalences of 15–30 % [1], serious ulcer complications occur in about 2–4 % annually [1–4], and an increased incidence of stroke, myocardial infarction (MI), and congestive heart failure has also been reported with many NSAIDs [5, 6].

Among the known risk factors for CV toxicity with NSAID treatment are older age, hypertension, and established CV disease [7, 8]. Risk factors for NSAID-associated GI complications include older age, history of ulcers or upper GI (UGI) symptoms, and concomitant use of such medications as anticoagulants and low-dose aspirin (LDA) [9, 10]. Twenty percent of NSAID users are estimated to take concomitant LDA, usually as prophylaxis for CV events [11].

A recommended strategy to prevent higher risk patients from developing NSAID-associated ulcers is the concomitant administration of a gastroprotective agent, for example, a proton pump inhibitor (PPI) [2, 12–16]. PPIs have also been shown to reduce the risk for GUs, duodenal ulcers (DUs), and their complications associated with the continuous use of LDA [17–19].

However, despite recommendations from guidelines, several studies suggest that, although increasing, use of concomitant gastroprotective agents with NSAIDs remains low [20–24].

As a potential solution to the under-use of gastroprotective agents, a fixed-dose combination of enteric-coated (EC) naproxen 500 mg and immediate-release (IR) esomeprazole magnesium 20 mg (naproxen/esomeprazole magnesium; NAP/ESO) has been designed to provide sequential delivery of, first, a PPI, and then an NSAID from a single tablet. Phase III trials have demonstrated comparable efficacy for NAP/ESO and celecoxib in the treatment of OA of the knee [25], while NAP/ESO was associated with a significantly lower incidence of endoscopic GUs compared with EC naproxen in patients at risk for developing NSAID-associated ulcers [26]. Furthermore, long-term (12-month) use of NAP/ESO was not associated with any new safety issues, including predefined UGI and CV adverse events (AEs) [27]. The NAP/ESO combination is currently licensed in both the United States and Europe for the relief of signs and symptoms of OA, RA, and ankylosing spondylitis, and to decrease the risk for developing NSAID-associated GUs in at-risk patients [28, 29].

The regulatory studies with the NAP/ESO combination tablet included a substantial number of patients who were also taking LDA, reflecting the frequency with which such dual NSAID/LDA therapy occurs in routine clinical practice. In order to explore the possible GI and CV effects of combining LDA with either the combination tablet or other NSAID, prespecified analyses of ulcer incidence in patients stratified by LDA use were conducted and AE data from all 5 Phase III studies were pooled in a post hoc analysis of the safety and tolerability of NAP/ESO.

Patients and methods

Studies

The study designs of the 5 Phase III studies included in this analysis have been reported previously [25–27]. Briefly, studies 301 (NCT00527787) and 302 (NCT01129011) were identically designed 6-month, randomized, double-blind, parallel-group studies comparing NAP/ESO and EC naproxen tablets in patients who were at risk of developing GUs [26]. The primary endpoint was the cumulative incidence of patients with endoscopically observed GUs (≥3 mm diameter with depth) at any time throughout the 6 months of treatment. Studies 307 (NCT00664560) and 309 (NCT00665431) were identically designed 3-month, randomized, double-blind, placebo-controlled, parallel-group studies comparing NAP/ESO, celecoxib, and placebo, whose primary aim was to assess efficacy in pain relief of these agents in patients with OA of the knee, using the Pain and Function Subscales of the Western Ontario and McMaster Universities (WOMAC) OA index and the patient global assessment of OA questionnaire [25]. Study 304 (NCT00527904) was a 12-month, open-label, multicenter study assessing the safety of NAP/ESO in patients with OA, RA, or other conditions requiring daily NSAIDs for at least 12 months and at risk of GI events [27]. For all studies, data were collected on treatment-emergent AEs, serious AEs (SAEs), AEs leading to discontinuation, and predefined NSAID-associated UGI AEs. In addition, studies 301, 302, 307, and 309 included an assessment of tolerability endpoints, such as heartburn resolution, severity of dyspepsia assessment (SODA) or modified SODA (mSODA), and rescue antacid use, while study 304 collected data on heartburn and dyspepsia as AEs, alongside exposure to, and dosage of, acetaminophen [25–27].

Patients

The five studies enrolled patients with OA, RA, ankylosing spondylitis, or another condition expected to require chronic daily NSAID therapy. Studies 307 and 309 included patients with OA of the knee only. Eligible patients were aged 50 years or over. In addition, studies 301, 302, and 304 also permitted younger patients (aged 18–49 years) provided they had a history of uncomplicated GU or DU within the previous 5 years. The use of LDA (defined as ≤325 mg/day) was allowed at the discretion of the treating physicians in all studies. Among the key exclusion criteria were uncontrolled or unstable cardiac disorder, prior GI disorder or surgery leading to impaired drug absorption, allergic reaction, or intolerance to any PPI or any NSAID (including aspirin). In the endoscopic studies (301 and 302), patients had to be ulcer-free at a baseline endoscopy.

Study treatment

In studies 301 and 302, patients received either oral NAP/ESO (EC naproxen 500 mg/IR esomeprazole 20 mg) twice daily or oral EC naproxen 500 mg twice daily. In study 304, patients received oral NAP/ESO twice daily as described for studies 301 and 302. In studies 307 and 309, patients received oral NAP/ESO twice daily, celecoxib 200 mg twice daily, or placebo.

Treatment was discontinued if patients withdrew informed consent, were judged by the investigator to be at significant safety risk, became pregnant, had a creatinine clearance of <30 mL/min, or had a confirmed decrease in hemoglobin level of >2.0 g/dL. In addition, in studies 301, 302, and 304, treatment was discontinued if patients developed an ulcer.

Incidence of ulcers

Studies 301 and 302 assessed GUs and DUs using endoscopy. Data from these two studies were pooled in a predefined analysis to assess the effect of NAP/ESO plus concomitant LDA use on the incidence of GUs and DUs.

Safety

AEs and SAEs occurring from the start of the study drug administration to the end of each study were recorded and coded using preferred terms from the Medical Dictionary for Regulatory Activities (MedDRA) version 10.1. Overall, AE and SAE data were pooled across all five studies for all patients who received ≥1 dose of study drug). For the purpose of comparing safety across all five studies, a data cut-off of 120 days was used for studies 301, 302, and 304. For consistency across the studies, AEs identified via endoscopy were excluded in this analysis.

CV events were prespecified in study 304 and were compiled by the sponsor's physician and an independent cardiologist based on literature and medical expertise. This compilation was used for all the other studies. All CV AE data were pooled across all five studies and presented according to LDA users and non-users.

Statistical analyses

Overall, AE and SAE data were stratified by subgroups of LDA users and LDA non-users and pooled for post hoc analysis. Patients who were taking LDA at any time during the study period for a particular study were considered to be an LDA user. The incidence of an event refers to the proportion of patients who reported that event, and not the number of occurrences of that event.

A summary of the cumulative observed incidence of GUs and DUs at 1, 3, and 6 months was produced based on the intent-to-treat (ITT) population in studies 301 and 302 (i.e., all patients who received ≥1 dose of study drug and had no ulcer as detected by endoscopy at screening); however, the ITT and safety populations were identical in these two studies. Safety analyses were based on safety populations (all patients who received ≥1 dose of study drug) in each study. The incidences of endoscopically observed GU and DU, and incidences of AEs of erosive gastritis and erosive duodenitis, were analyzed using pooled data from studies 301 and 302 for the prespecified subgroups of LDA users and LDA non-users.

The incidence of prespecified NSAID-associated UGI AEs (including dyspepsia, abdominal discomfort, gastritis, and vomiting; Table 1), and discontinuation rates due to any AE or a prespecified NSAID-associated UGI AE, were summarized by LDA subgroup in the pooled safety populations of all five studies.

In order to accurately compare the safety results across the treatment groups in the five studies, which had varying study lengths and AE identification methods (e.g., use or non-use of endoscopy), AEs starting >120 days after the first dose of study medication in studies 301, 302, and 304 were not included in these summaries, nor were AEs identified during an endoscopy in studies 301 and 302.

Statistical summaries were completed using Statistical Analysis System (SAS) version 8.

Results

Patients

Overall, 2,317 patients were treated across the five studies, and 1,790 patients completed the studies (Fig. 1). Treatment arms within the individual studies were well-balanced

Table 1 Prespecified NSAID-associated upper gastrointestinal adverse events reported across all five studies

Abdominal discomfort	Esophageal discomfort	GI hemorrhage
Abdominal pain	Esophageal disorder	GI mucosal disorder
Abdominal tenderness	Esophageal hemorrhage	Hematemesis
DU	Esophageal stenosis	Hemorrhagic duodenitis
Duodenal hemorrhage	Esophageal ulcer	Hemorrhagic gastritis
Duodenal scarring	Esophageal varices	Hyperchlorhydria
DU hemorrhage	Esophagitis	Nausea
Duodenitis	Gastric hemorrhage	Reflux esophagitis
Dyspepsia	Gastric mucosal lesion	Stomach discomfort
Epigastric discomfort	Gastritis	Upper abdominal pain
Erosive duodenitis	GERD	Vomiting
Erosive esophagitis	Gastro-esophagitis	
Erosive gastritis	GI erosion	

Adapted from Goldstein et al. [26] *Aliment Pharmacol Ther* 2010 with permission from John Wiley and Sons

DU duodenal ulcer, *GERD* gastro-esophageal reflux disease, *GI* gastrointestinal, *NSAID* nonsteroidal anti-inflammatory drug

and baseline demographics and characteristics were similar for patients within studies [25–27]. Table 2 shows the baseline demographics and patient characteristics by LDA subgroup. Across the five studies, 4.8 % of patients had a previous history of ulcer, while 55.7 % of patients had a previous history of CV events.

Overall, 1,157 patients were treated with NAP/ESO. Of these, 298 were identified as taking concomitant LDA (≤325 mg/day) during the study (99 patients in studies 301 and 302 combined, 124 patients in studies 307 and 309 combined, and 75 patients in study 304). Of the 298 patients who were identified as taking NAP/ESO and concomitant LDA, an average daily LDA dose could be calculated for 292 patients. An LDA dose of ≤ 100 mg/day was received by 240 (80.5 %) of the NAP/ESO patients, while 52 (17.4 %) patients received a dose of 101–325 mg/day.

The average daily LDA dose could not be determined for 11 of the LDA users ($n = 6$ in the NAP/ESO group; $n = 1$ in the placebo group; $n = 4$ in the EC naproxen group); for these patients, the LDA dose was classified as either "dose not recorded" or "unable to determine".

Of the patients who were determined to be LDA users, 3 patients (1 in the EC naproxen group of study 301, 1 in the EC naproxen group of study 302, and 1 in the NAP/ESO group of study 304) were originally classified as LDA non-users in the study-level analyses reported elsewhere, as the medication they were taking (Aggrenox or BC Powder) was not among the original LDA search terms. Two of these patients received an LDA dose of ≤100 mg/day, while the third had their LDA dosage classified as "other".

The median durations of exposure to NAP/ESO were 178.5, 85, and 349 [27] days in the safety populations for studies 301 and 302 combined, 307 and 309 combined, and study 304, respectively.

Incidence of ulcers

The cumulative incidence of GUs at month 6 by LDA use subgroup in studies 301 and 302 has been published previously [26]. This publication reported that NAP/ESO was associated with a significantly lower incidence of GUs than EC naproxen, irrespective of concomitant LDA use (3.0 vs 28.4 %, respectively in LDA users and 6.4 vs 22.2 %, respectively in LDA non-users; $P < 0.001$ in favor of NAP/ESO in both subgroups) [26]. The reclassification of two patients' LDA status for this analysis did not substantially alter these findings: incidence of GUs with NAP/ESO vs EC naproxen in LDA users was 3.0 vs 27.9 %, respectively, and incidence in LDA non-users was 6.4 vs 22.4 %, respectively.

Among LDA users, the cumulative observed incidences of GUs at 1, 3, and 6 months in NAP/ESO-treated patients were low and substantially less than those observed for EC naproxen-treated patients (Fig. 2); the cumulative observed incidences of DUs among patients receiving NAP/ESO and concomitant LDA were also low and less than those observed for EC naproxen-treated patients (Fig. 2). Similar trends in the incidence of GUs and DUs were observed in the LDA non-user group at 1, 3, and 6 months (Fig. 2).

Incidence of erosive gastritis and erosive duodenitis

Overall, erosive gastritis was reported as an AE in fewer NAP/ESO-treated patients than EC naproxen-treated patients [19.4 % (83/428) vs 38.0 % (162/426), pooled analysis of data from studies 301 and 302; Chi squared $P < 0.001$]. Among LDA users, the incidence of erosive gastritis was significantly higher in the EC naproxen group compared with the NAP/ESO group [36.5 % (38/104) vs 18.2 % (18/99); Chi squared $P = 0.0046$]. A similar finding was observed for incidence of erosive gastritis among LDA non-users [38.5 % (124/322) vs 19.8 % (65/329) for EC naproxen and NAP/ESO, respectively; Chi squared $P < 0.001$]. Of the patients who had erosive gastritis, 4 (0.9 %) patients in the NAP/ESO treatment group (all LDA non-users) and 39 (9.2 %) patients in the EC naproxen group (12 LDA users and 27 LDA non-users) also had a GU.

The incidence of erosive duodenitis was also lower among patients treated with NAP/ESO than those receiving

EC naproxen [2.1 % (9/428) vs 11.7 % (50/426), pooled analysis in studies 301 and 302; Fisher's exact $P < 0.0001$]. Among LDA users, the incidence of erosive duodenitis was lower for the NAP/ESO group than the EC naproxen group [2.0 % (2/99) vs 5.8 % (6/104)]. However, the test for differences was not significant (Fisher's exact $P = 0.28$). Among LDA non-users, rates of erosive duodenitis were significantly lower for patients in the NAP/ESO group than the EC naproxen group [2.1 % (7/329) vs 13.7 % (44/322), respectively; Fisher's exact $P < 0.0001$]. Only one patient across both studies experienced both erosive duodenitis and a DU (an EC naproxen-treated patient in the LDA non-user group).

Safety

Adverse events

Among LDA users across all 5 studies, the incidence of reported AEs was similar across all treatment groups; 56.0 % (167/298) of NAP/ESO-treated patients reported AEs compared with 58.7 % (61/104) of EC naproxen-treated patients, 53.8 % (56/104) of celecoxib-treated patients, and 57.1 % (32/56) of placebo-treated patients. Among LDA non-users, the corresponding incidences were also similar across treatment groups: 54.9 % (472/859) for NAP/ESO; 59.6 % (192/322) for EC naproxen; 48.4 % (186/384) for celecoxib; and 49.5 % (94/190) for placebo (Table 3). GI disorders were the most commonly reported AEs in patients treated with NAP/ESO; the most common GI AE was dyspepsia (Table 3).

Among LDA users, the incidences of prespecified NSAID-associated UGI AEs were lowest for NAP/ESO [16.1 % (48/298)], highest for EC naproxen [31.7 % (33/104)], and were 22.1 % (23/104) for celecoxib, and 23.2 % (13/56) for placebo. The difference between NAP/ESO and EC naproxen was statistically significant (Chi squared test, $P = 0.001$). The most common prespecified NSAID-associated UGI AEs were dyspepsia, nausea, and upper abdominal pain (Table 4). Among LDA non-users, prespecified NSAID-associated UGI AEs were observed in 20.3 % (174/859) of NAP/ESO-treated patients, 36.6 % (118/322) of EC naproxen-treated patients (the highest incidence amongst the treatments considered), 18.5 % (71/384) of celecoxib-treated patients, and 18.9 % (36/190) of

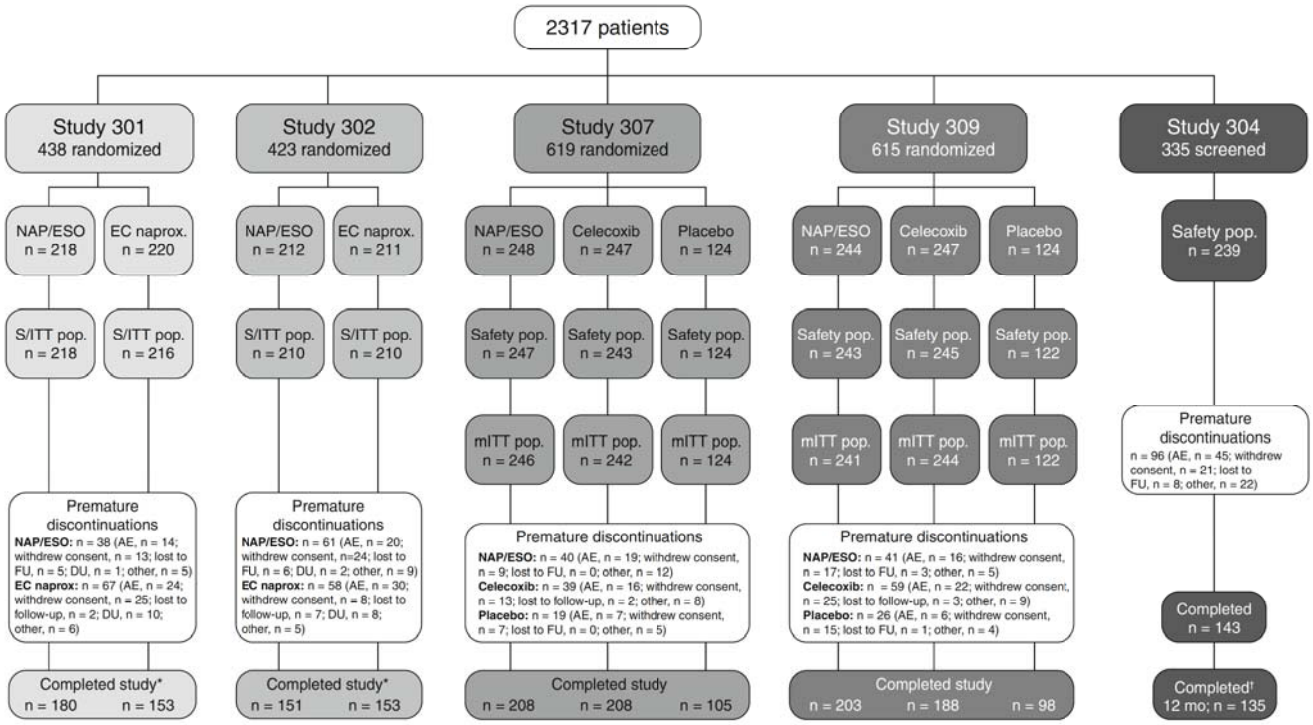

Fig. 1 Patient disposition in the five studies. *AE* adverse event, *DU* duodenal ulcer, *EC* enteric-coated, *FU* follow-up, *ITT* intent-to-treat, *mo* month, *mITT* modified intent-to-treat, *NAP/ESO* naproxen/esomeprazole magnesium, *naprox.* naproxen, *pop.* population, *S* safety. *Patients completed 6 months of study treatment or discontinued due to gastric ulcer. †Patients completed ≥348 days on study treatment

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