Clinical studies with Krka's proton pump inhibitors in the treatment of gastroesophageal reflux disease reviewed

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Key words
Gastroesophageal reflux disease, proton pump inhibitor, quality of life, safety, PAN-STAR, WIN

Abstract
Proton pump inhibitors (PPIs) are the most effective treatment against gastroesophageal reflux disease (GERD), which is one of the most common diseases encountered in gastroenterology. Clinical studies with Krka's omeprazole, lansoprazole and pantoprazole have confirmed their high efficacy and good tolerability in the treatment of GERD in real clinical setting. Krka's PPIs improve the health-related quality of life by relieving the patient of disturbing and limiting GERD symptoms. Patients with GERD have been shown to benefit from prolonging therapy from 4 to 8 weeks. In patients that need maintenance therapy, continuous maintenance therapy better prevents relapses of GERD than on-demand therapy. It has also been observed that patients with erosive reflux disease respond better to PPI therapy than patients with non-erosive reflux disease. Importantly, these results from Krka's phase IV studies support the optimisation of the management of GERD.

Introduction

Gastroesophageal reflux disease (GERD) is one of the most common diseases encountered in gastroenterology, with a prevalence of up to 30%. In industrially developed countries the prevalence of GERD is usually around 20%. The incidence of the disease is around 5 per 1,000 patient-years.[1] According to the Montreal definition, GERD is a condition which develops when the reflux of stomach contents causes disturbing symptoms and/or complications.[2] The main symptoms that are also used for the diagnosis of GERD are heartburn and acid regurgitation. The population with GERD is experiencing heartburn regularly: 43% as often as once or twice a week and 24% once or several times daily.[3] The high prevalence of the disease has potentially serious social consequences since the pain and discomfort caused by GERD have a negative impact on health-related quality of life, increase the absence from work and decrease work productivity.[4, 5, 6] The presence of GERD affects the individual's sense of well-being as health is a state of complete physical, mental and social well-being.[7] In the great majority of patients with GERD, the disease does not lead to complications, but presents itself with often severe symptoms. Some 60% of primary care patients with disturbing reflux symptoms have no endoscopically recognisable lesions of the esophageal mucosa and 35% have erosive esophagitis (75% of the cases are mild, corresponding to Los Angeles (LA) classification grade A/B, and 25% are severe, corresponding to LA classification grade C/D). In about 5% of the patients, complications, such as stricture, ulcer and in particular Barrett's esophagus or even adenocarcinoma, must be expected.[8] Epidemiological data support the hypothesis that GERD is not a spectrum disease with occasional reflux symptoms without lesions at the one end, and severe complications at the other, but can instead be classified into three distinct categories – non-erosive

reflux disease (NERD), erosive reflux disease (ERD), and Barrett's esophagus – in each of which the patient usually remains, meaning that progression of the disease over time is, overall, very rare.[9]
There are several causes for reverse flow of gastric juice into the esophagus. The most important factors contributing to the development of the disease are too frequent spontaneous relaxations of the lower esophageal sphincter and hiatal hernia, which allow backflow of acid, pepsin, and bile salts into the esophagus, and impaired esophageal clearing (propulsive peristalsis and saliva).[10, 11, 12]
The most effective medications currently used for the treatment of GERD patients are PPIs.[13, 14]
Since GERD is a chronic condition, withdrawal of a PPI very often results in relapse. The rate of relapses is 80% to 90% in 6 to 12 months.[15, 16, 17] This led to the introduction of several therapeutic options, from on-demand PPI therapy and intermittent therapy, used only when problems occur, to continuous maintenance regimens. If maintenance therapy is administered, a PPI can be used at the standard dose or at half of the standard dose. Maintenance therapy leads to a reduction or elimination of symptoms and to an improvement in the health-related quality of life, and it has a favourable cost-benefit ratio.[18]
Krka is one of the few pharmaceutical companies offering five different PPIs for treatment of GERD: omeprazole (Ultop), lansoprazole (Lanzul[A]), pantoprazole (Nolpaza[B]), esomeprazole (Emanera[C]) and rabeprazole (Zulbex[D]). Ultop was introduced on the market in 1989 and was made available to patients in Europe as one of the first PPIs, at that time a totally new class of medicines in the treatment of acid related disorders.[19]
Up until now several clinical studies have been performed with Krka's PPIs in patients with acid related disorders. These clinical studies demonstrated the efficacy and safety of Krka's PPIs in more than 9,000 patients in 11 countries. Around 4,000 of these patients have been treated with Nolpaza.
In this article we will focus on three phase IV clinical trials with Krka's omeprazole, lansoprazole or pantoprazole in the management of GERD. The efficacy and safety of Krka's PPIs in the treatment of GERD are evaluated and the following treatment aspects are addressed:

- the influence of the duration of PPI treatment on the management of GERD,
- which maintenance therapy approach prevents relapse of GERD better,
- the differences in response to therapy between patients with ERD and GERD,
- the effect of PPIs on health-related quality of life.

Maintenance therapy of gastroesophageal reflux disease patients with omeprazole

This study was conducted to clarify which approach to maintenance treatment should be used in specific groups of GERD patients and which dose of a PPI might be most suitable for life-long maintenance therapy.[20] The aim of this study was to establish the efficacy of maintenance therapy (confirmed by endoscopic evidence, or symptomatically in the case of NERD) in patients with different grades of GERD receiving on-demand PPI therapy or continuous therapy with low or standard doses of PPIs. Krka's omeprazole (Ultop) was used as PPI therapy.
This study was designed as a prospective, stratified, randomised study and was conducted in 24 specialist out-patient clinics and hospital centers in Slovenia. Included were 216 patients meeting the criteria for GERD, both ERD and NERD, that successfully completed acute therapy with omeprazole.
Acute therapy in all patients with ERD consisted of omeprazole 20 mg (LA grades A and B) or 40 mg once daily (LA grades C and D). If endoscopic cure was not achieved at 8 weeks, treatment was continued for another 8 weeks with 40 mg of omeprazole once daily, and endoscopy was again used to confirm healing.

Acute therapy of patients with NERD consisted of 20 mg of omeprazole for 8 weeks. If healing was not achieved, treatment was continued for another 8 weeks with omeprazole 40 mg once daily.

[C] The product is marketed under different brand names in different countries (Lanzul, Lansoptol, Lanso TAD).
[D] The product is marketed under different brand names in different countries (Nolpaza, Appryo).
[E] The product is marketed under different brand names in different countries (Emanera, Emozul, Escadra).
[F] The product is marketed under different brand names in different countries (Zulbex, Gelbra).

In this patient group, the criteria for cure were the absence of a predominant symptom (heartburn, regurgitation) over the past 7 days prior to the end-of-study visit or the presence of a predominant symptom of mild severity for 1 day at the longest, of grade 1 on a scale graded from 0 to 3.
Patients cured after 8 to 16 weeks with acute treatment of GERD entered into a maintenance treatment phase.
Patients with NERD and those with mild ERD (LA grade A and LA grade B) were randomly assigned to group A1 or A2. Group A1 and A2 differed from each other in the treatment approach to maintenance therapy. Group A1 patients were allocated to on-demand therapy with omeprazole 20 mg (taken for not more than 3 consecutive days and not more than twice in 3 months). Group A2 patients received continuous therapy with omeprazole 10 mg daily. Patients with ERD LA grade C and LA grade D were allocated to group B and treated with 20 mg of omeprazole daily. Clinical control visits were scheduled every 3 months. The last visit, at 12 months, included mandatory gastroscopy (see Figure 1). In cases of suspected relapse, additional control visits and gastroscopy were done outside the regular schedule.

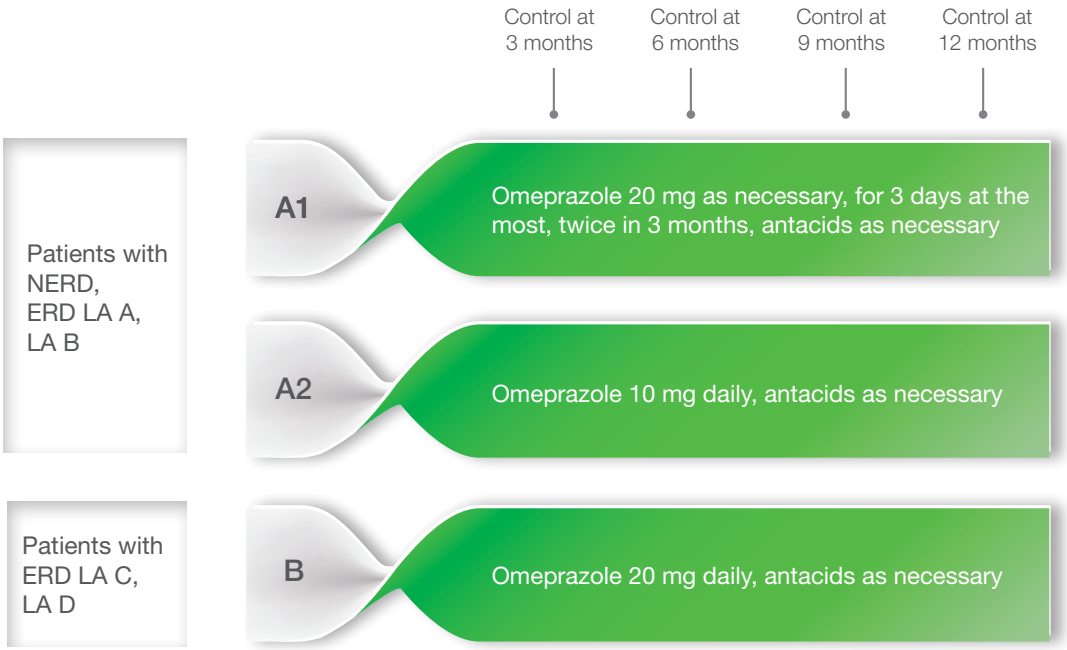

Figure 1. Chart of patient allocation to groups and 12-month follow-up protocol

Ninety-four patients were allocated to group A1, 102 to group A2, and 20 to group B. In the intention-to-treat analysis, the cumulative relapse rate at 12 months was 42.5% in group A1, 29.4% ($p < 0.05$) in group A2, and 40% in group B. None of the patients experienced serious adverse events during the study period.
In the population of 31 patients with NERD in group A1, 15 (48.4%) patients were in remission after 12 months and in group A2, 19 (76%) from 25 patients. The difference was of statistical significance ($p < 0.05$). A statistically significant difference ($p < 0.001$) in favour of patients on the continuous maintenance regimen with 10 mg of omeprazole was also found between groups A1 and A2 in patients with GERD LA grade A. In patients with GERD LA grade B no statistically significant differences were found between the groups ($p > 0.05$).
Of the 20 patients in group B, 12 (60%) were in remission after 12 months.
Patients evaluated the health-related quality of life on a visual analogue scale from 1 (worst quality of life) to 10 (best quality of life). The evaluation results at 12 months are shown in Figure 2. The mean score of health-related quality of life at the end-of-study visit at 12 months was 9.4 in group A1, 9.7 in group A2, and 9.8 in group B. The differences between the groups were statistically non-significant.

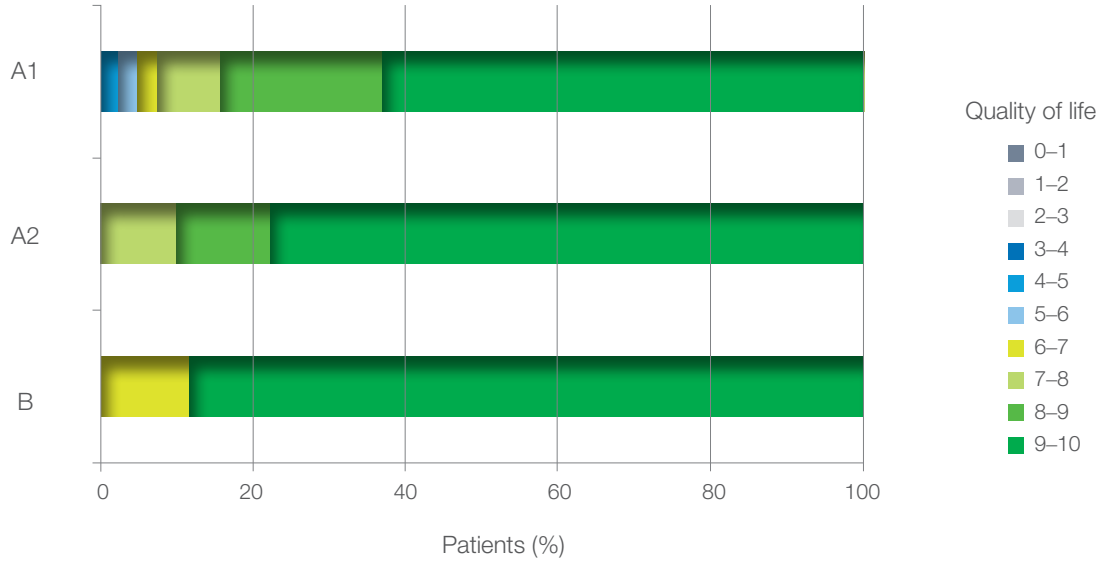

Figure 2. Quality-of-life evaluation at 12 months by treatment group

Adverse events were the reason for treatment discontinuation in only one patient in group B.
Patients with NERD and those with ERD need maintenance therapy, because GERD is a chronic disease with frequent relapses. To manage relapses there was the option of on-demand therapy or continuous therapy in this study. The results of this study have demonstrated that continuous therapy with a 10 mg maintenance dose of omeprazole leads to a statistically significantly lower relapse rate than on-demand therapy with 20 mg of omeprazole in patients with NERD or ERD LA grade A. Krka's omeprazole was well tolerated by the patients and associated with a very high health-related quality of life score in all three groups (A1, A2 and B), varying from 9.4 to 9.8.
According to Tepeš et al., patients with a more severe type of ERD (LA grade C, LA grade D) and also patients with LA grade B, usually require life-long continuous maintenance therapy with standard doses of PPIs (for example omeprazole 20 mg). At least one third of patients with LA grade C and LA grade D also experience a relapse, usually asymptomatic, with this continuous maintenance therapy. These patients require a continuous maintenance regimen with higher doses of PPIs, preferably administered twice daily.[20] Later studies have confirmed this finding making this strategy part of the latest guidelines for the diagnosis and management of GERD, with the aim to use the lowest effective dose for patients that require long-term PPI therapy.[13]

What is Important in the treatment of Non-erosive reflux disease (WIN) – study with lansoprazole

In contrast to the previous study with Krka's omeprazole this prospective, comparative, controlled, stratified, randomised multicenter study investigated only NERD patients. Patients were not only followed during the acute phase of the treatment, but also relapses were followed until 3 months after reaching healing criteria and stopping therapy with Krka's lansoprazole. The primary goals of this study that took place in Slovenia and Croatia were to demonstrate the efficacy of Krka's lansoprazole (Lanzul) in NERD patients, to study the effect of therapy duration on treatment outcome and to observe the number of relapses after stopping therapy. Secondary goals were to establish the effect of dose and length of therapy with lansoprazole on treatment outcome in NERD patients, safety of therapy with lansoprazole and its influence on the quality of life.
Lansoprazole was the second PPI approved for clinical use. Krka's lansoprazole was first released on the market in 1997.
In the acute treatment phase of GERD, patients were treated with lansoprazole for 4 to 8 weeks. After stopping acute therapy the patients were followed for 3 months. Before the start of the treatment

all patients underwent endoscopy and only patients without erosive esophagitis were included in the study. The selected NERD patients were split into two groups: group A1 was treated with capsules of Lanzul S (lansoprazole, 15 mg) and group A2 with capsules of Lanzul (lansoprazole, 30 mg).
During acute treatment phase the initial visit was followed by a first control visit after 4 weeks, second control visit 2 weeks later and the third control visit after another 2 weeks. Patients were assessed for reaching healing criteria after 4 (first control visit), 6 (second control visit) or 8 weeks of treatment (third control visit). Patients that were not successfully treated after 8 weeks of treatment continued therapy according to the doctrine.
Reaching healing criteria in the acute treatment phase was defined as the absence of predominant symptoms (heartburn or regurgitation) during the last 7 days before the control visit/or its presence on not more than 1 day in the last week before the control visit, but in a mild form; no other symptom was allowed to be more marked than it was at the beginning of the treatment; i.e. must not have been severe.
Only the patients that reached healing criteria in the acute treatment phase were included in the second phase of the study to follow relapse after quitting therapy. The first control visit in the second phase of the study took place after 4 weeks and the second control visit 8 weeks after the first one. At each control visit patients evaluated the severity of symptoms, occurrence of adverse events and the quality of life.
In the second phase of the study relapses were defined as having 2 to 3 reflux episodes per hour that lasted for more than 5 minutes and occurred more often than on 1 day in a week or reflux symptoms that lasted more than 1 hour per day and occurred more often than on 1 day in a week.
In the acute phase of the treatment 211 patients were included of which 187 (88.6%) were successfully treated. Most of them reached the healing criteria after the first control visit (47.8%). At the second control visit a further 18.5% of patients reached the healing criteria and at the third control visit another 22.3% (see Figure 3).

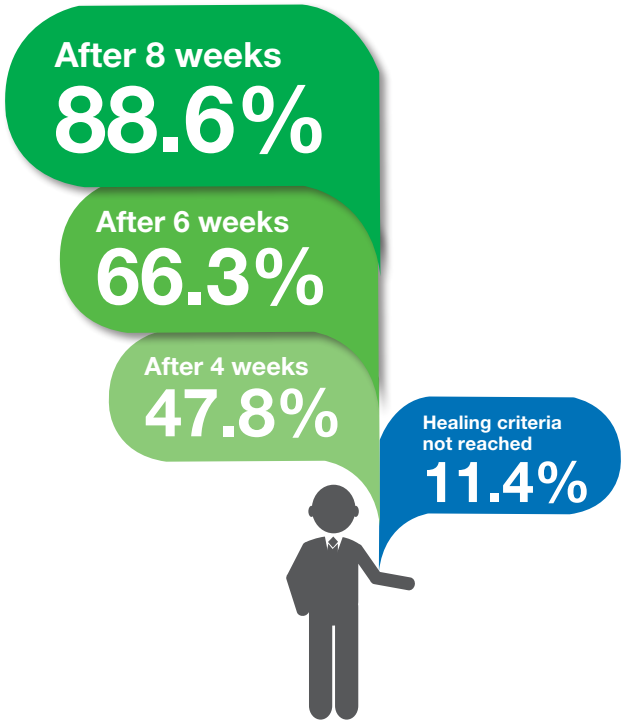

Figure 3. Percentage of patients reaching healing criteria in the acute treatment phase (n = 211)

Although not all patients reached the healing criteria, the severity of all symptoms was substantially lowered.

One hundred and eighteen patients were included in the second phase of the study following relapses of GERD. The other 69 patients, although they also reached the healing criteria, did not want to cooperate during the second phase of the study. One hundred and one patients (85.6%) successfully concluded the second phase of the study without relapses. Relapses were reported in 12.7% of the patients, more precisely in 12 patients (10.2%) at the first control visit of the second phase (fourth control visit during the whole study) and in 3 patients (2.5%) at the second control visit during the second phase of the study (fifth control visit) (see Figure 4).

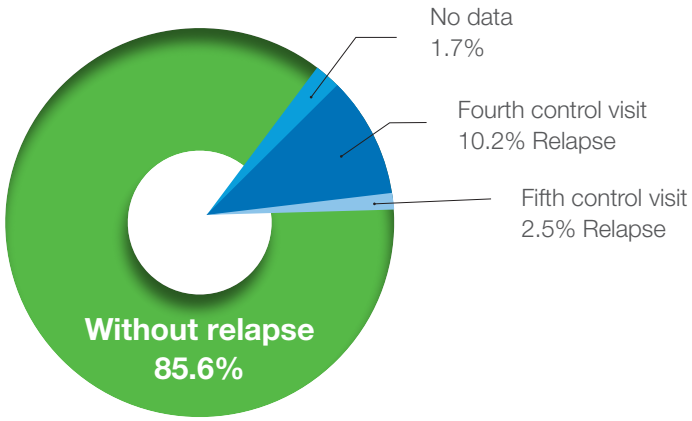

Figure 4. Percentages of patients with relapse in second phase of the study after stopping study medication (n = 118)

At the start of the study patients evaluated their quality of life as 5.4 and at the end of the study as 9.3 on the scale of 10. There was no difference between the two treatment groups (see Figure 5).

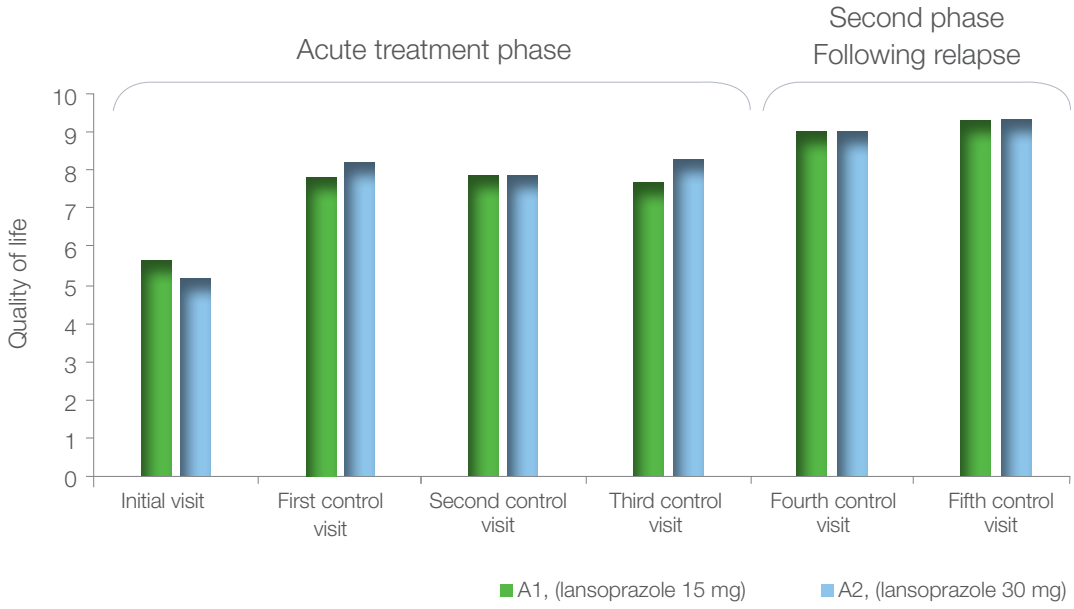

Figure 5. Evaluation of the quality of life in both treatment groups

A comparison between group A1 (15 mg lansoprazole) and group A2 (30 mg lansoprazole) in the acute treatment phase, demonstrated that 85.1% and 92.3% of the patients, respectively, reached the healing criteria. There were no significant differences between the treatment groups.
After the fifth control visit (second control visit during the second phase of the study) 87.9% of the patients in group A1 stayed in remission and 83.3% of the patients in group A2, but the difference did not reach significance.

In both groups the greatest decrease in predominant symptoms, heartburn and regurgitation, was achieved after 4 weeks of treatment.
Twelve patients (5.5%) experienced adverse events related to the study medication. Eight patients stopped study treatment because of adverse events.

On the basis of the results in this study we can conclude that 8 weeks of treatment of NERD patients instead of 4 weeks should be supported, because in this time interval an additional 40.8% of patients reached healing criteria. The difference in dosage of Krka's lansoprazole had no influence on treatment outcomes of NERD patients in this study.
The study confirmed that a majority of NERD patients reached healing criteria with both strengths of Krka's lansoprazole; 92.3% of NERD patients with lansoprazole 30 mg and 85.1% of patients with lansoprazole 15 mg (p = n.s.).
During the 3 months of observation of relapse, 85.6% of the patients stayed in remission, which means that the effect of Krka's lansoprazole was maintained in a large proportion of patients for up to 3 months after stopping the treatment.
Patients evaluated their quality of life as being substantially better after treatment with Krka's lansoprazole, with a score higher than 9, which means that the study medication made it possible for NERD patients to live without disturbing and limiting symptoms.
The safety of Krka's lansoprazole was confirmed by the observation that adverse events occurred only rarely.

Meta-analysis of the efficacy and safety of PANtoprazole in the treatment and SympTom relief in patients with gAstRoesophageal reflux disease (GERD) – PAN-STAR

The PAN-STAR studies, three studies with a similar protocol that were concluded in 2013 in the Russian Federation, Poland and Slovenia, were analysed in a meta-analysis. All three studies were designed as multicenter, open labelled, prospective phase IV studies.
The PAN-STAR studies investigated both ERD and NERD patients that were treated 4 to 8 weeks with pantoprazole (Nolpaza 40 mg). This is in line with the latest guidelines on the diagnosis and management of GERD that recommend 8 weeks of treatment in patients with ERD with a PPI.[13]
In literature it has been described that patients with NERD are more difficult to manage than those with erosive esophagitis and that progression in erosive esophagitis is a relatively uncommon occurrence.[21] NERD patients need longer treatment to reach relief of symptoms. Although the PPIs are effective medicines, 17 to 32% of GERD patients have resistant symptoms of heartburn and regurgitation regardless of PPI therapy.[22] PPIs are accepted as the main therapy for GERD as they have not only shown to be superior over histamine$_2$ receptor antagonists in patients with ERD, but also in patients with NERD.[13, 23] In different clinical studies using different PPIs, complete disappearance of clinical symptoms at 8 weeks of treatment was reported in 65 to 75% of the treated patients, and endoscopic cure was observed in 85 to 90% of the patients. Thus, the endpoint of healing is easier to accomplish than the endpoint of complete symptom relief.[24]
Pantoprazole was the third PPI approved for clinical use. Krka's pantoprazole was first released on the market in 2007.
The meta-analysis of the PAN-STAR studies adds to the clinical evidence on how to optimally treat GERD patients.
Three clinical trials with similar protocols were performed in Slovenia, the Russian Federation and Poland. The study population (n = 252) was selected according to typical GERD symptoms (heartburn/regurgitation), which were disturbing for the patient. Prior to the start of the study, upper endoscopy had been performed in all patients. The patients included into the study were divided into two groups, depending on the presence or absence of reflux esophagitis.
All patients started treatment with one tablet daily of Nolpaza 40 mg. If the patient did not fulfill the healing criteria (absence of the primary symptom, heartburn or regurgitation during the last 7 days

before the control visit/or its presence on not more than 1 day in the last week before the control visit, but in a mild form; no other symptom that is more marked than it was at the beginning of the treatment; i.e. not severe) after 4 weeks of treatment, the treatment with Nolpaza 40 mg was continued for another 4 weeks. At the end of the study after 8 weeks the control visit of both groups of patients (patients in remission and patients treated with Nolpaza 40 mg for 8 weeks) was performed. The primary endpoint was the effect of pantoprazole (Nolpaza 40 mg) on the healing of ERD and NERD patients. Secondary endpoints were the effect of therapy on the quality of life and quantification of the rate of adverse events associated with pantoprazole treatment.
In 117 (46%) patients no endoscopically detectable changes of the esophageal lining were found, meaning that they did not have esophagitis. On the day of enrolment half of the patients already had reflux disease for 1 to 2 years, 4% of the patients for more than 2 years and others up to 12 months. The results of the PAN-STAR studies show that Nolpaza 40 mg is highly effective in the treatment of GERD. As many as 44% of all patients met the healing criteria after 4 weeks of treatment and 66% of all patients after 8 weeks of treatment. When comparing the number of ERD patients with that of NERD patients it was observed that after 8 weeks of treatment significantly more ERD patients reached healing criteria than NERD patients (71% vs. 60%; see Figure 6).

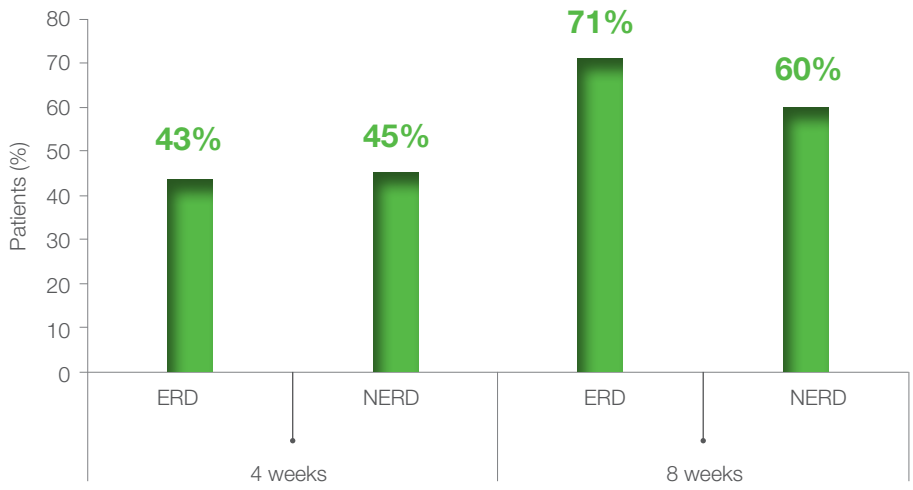

Figure 6. Erosive and non-erosive patients reaching healing criteria

The average total symptom severity score (sum of scores for each symptom assessed on the scale from 0 to 3) was significantly reduced after 4 weeks of treatment from 8.00 to 2.03, as assessed by 98.4% of the patients. After 8 weeks of treatment (including 40% of patients in remission, who completed treatment with Nolpaza 40 mg after 4 weeks of treatment), the average score was 1 as assessed by 93.6% of the patients.
The patients receiving Nolpaza for 4 weeks experienced a reduction of the predominant symptoms (heartburn and regurgitation) to an average total score of 1.11 (vs. 4.86 at baseline). After 8 weeks the average total score of the predominant symptoms further decreased to 0.54.
During the study the quality of life constantly and significantly improved. In patients that were already in remission after 4 weeks and stopped the study medication, the improvement in the quality of life was sustained, as assessed during the third visit after 8 weeks (see Figure 7).
Patients were shown to benefit from prolonging treatment from 4 to 8 weeks, as shown by more patients reaching the healing criteria (44% vs. 66%), further improvement of total symptoms severity score (2.03 vs. 1.00) and further improvement of the quality of life (7.61 vs. 8.41).

Figure 7. Quality of life (scale 1–10) in all patients and according to treatment duration

The same benefit from prolonging treatment from 4 to 8 weeks could be observed when considering patients with ERD and NERD separately. More patients reached the healing criteria after treatment was prolonged from 4 to 8 weeks in patients with ERD (43% vs. 71%) and patients with NERD (45% vs. 60%). The total symptoms severity score improved in patients with ERD (1.58 vs. 0.75) and NERD (2.56 vs. 1.28) and also the quality of life improved in patients with ERD (7.73 vs. 8.64) and NERD (7.47 vs. 8.15).

After 8 weeks the quality of life was slightly better in the group of erosive patients compared to the patients with NERD (8.64 vs. 8.15; $p < 0.05$).

Treatment with Nolpaza 40 mg was well tolerated, since more than 90% of patients were without adverse events throughout the study period. Adverse events with causal relationship appeared in total in 7.1% of the patients. Adverse events were assessed in 7.1% of the patients during the first period and only in 2 (0.8%) patients the adverse events persisted during the second period. The most common adverse events were constipation (5 patients, 2%), nausea (4 patients, 1.6%), flatulence (3 patients, 1.2%), hypersensitivity (3 patients, 1.2%) and headache (3 patients, 1.2%). Four patients discontinued the treatment due to adverse events related to Nolpaza treatment.

The results of the present meta-analysis show that Nolpaza 40 mg was associated with complete relief of GERD-related symptoms in the majority of patients with ERD and NERD. Furthermore, the severity of symptoms was also significantly reduced in patients without complete relief of symptoms. This meta-analysis not only confirms that Nolpaza 40 mg once daily is effective in the treatment of patients with GERD but also that it is well-tolerated, as 90% of the patients did not experience any adverse events during the study.

Already within 4 weeks Nolpaza significantly relieved symptoms and improved the quality of life of patients with GERD. Prolonging treatment from 4 to 8 weeks was beneficial for both groups, patients with ERD and patients with NERD, as more patients in both groups reached the healing criteria and experienced further relief of symptoms and improvement of the quality of life. In patients that were in remission already after 4 weeks and stopped the study medication both the relief of symptoms and the improvement in health-related quality of life were sustained at 8 weeks.
After 8 weeks significantly more patients with ERD reached the healing criteria compared to patients with NERD and the quality of life was slightly better in the group of erosive patients. This is in line with earlier observations that symptoms related to NERD are more difficult to manage.[21]

Conclusions

The three phase IV studies reviewed in this article demonstrate the efficacy and safety of Krka's PPIs, omeprazole (Ultop), lansoprazole (Lanzul) and pantoprazole (Nolpaza) in a clinical setting:

- Maintenance therapy with Krka's omeprazole prevented relapses of GERD.
- The WIN study showed that the high efficacy of Krka's lansoprazole was maintained in a large proportion of patients for up to 3 months after stopping therapy.
- The results of the PAN-STAR studies showed that Nolpaza 40 mg was highly effective in the treatment of GERD.
- In all three studies of this review the study medications were very well tolerated.

The following four conclusions from Krka's phase IV studies also show which treatment protocols are advisable to optimise the management of patients with GERD:

Patients with GERD benefit from prolonging therapy from 4 to 8 weeks

The WIN study with lansoprazole in patients with NERD and the meta-analysis of PAN-STAR studies with pantoprazole in patients with ERD and NERD showed the importance of prolonging GERD treatment from 4 to 8 weeks in the majority of patients. In the PAN-STAR studies with Nolpaza it was also proven that prolonging treatment from 4 to 8 weeks is beneficial for both patients with ERD and patients with NERD, as more patients in both groups reached the healing criteria and experienced further relief of symptoms and improvement of the quality of life.
Patients in remission already after 4 weeks of treatment (and stopping treatment) with Krka's pantoprazole had sustained improvement of symptoms at the control visit 4 weeks later.

Continuous maintenance therapy is superior over on-demand therapy in preventing relapses of GERD

GERD is a chronic condition with frequent relapses after stopping PPI therapy. The phase IV study with omeprazole has demonstrated that continuous therapy is better than on-demand therapy when choosing a PPI maintenance therapy to prevent a relapse in patients with NERD or ERD LA grade A. Patients with ERD LA B–D usually require life-long continuous maintenance therapy with standard doses of PPIs and one third of them that experience a (usually asymptomatic) relapse on such maintenance therapy need a higher PPI maintenance dose, preferably administered twice daily.[20]

Patients with ERD respond better to PPI therapy than patients with NERD

After 8 weeks significantly more patients with ERD reached the healing criteria compared to patients with NERD and the quality of life was slightly better in the group of erosive patients, as shown in the PAN-STAR studies with Nolpaza.

Krka's PPIs improve the quality of life of patients with GERD

All three studies have proven that Krka's PPIs relieve the disturbing and limiting GERD symptoms, which directly improves the health-related quality of life.

To conclude, the results of Krka's phase IV studies support the optimisation of the management of GERD.

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