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

Final report

Synopsis

KCT 27/2009 – PAN-STAR/PL

Author of the final report: Prof. dr hab. med. Andrzej Dąbrowski, Uniwersytecki Szpital Kliniczny in Białystok, Poland

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November 2013

1. INTEGRATED CLINICAL STUDY REPORT (TITLE PAGE)

Study title:
Efficacy and safety of **PAN**toprazole in the treatment and **S**ymp**T**om relief in patients with g**A**st**R**oesophageal reflux disease (GERD) – **PAN-STAR**

Name of the tested drug:
Nolpaza® 40 mg

Indication Studied:
- patients with reflux esophagitis
- patients with non-erosive reflux disease (NERD)

Study design:
This was a multicenter, prospective, open-label, phase IV study conducted in 2 medical centers in Poland. Patients were treated for 4 to 8 weeks (depending on fulfillment of healing criteria) with gastroresistant tablets Nolpaza® in a dose of 40 mg.
The study population consists of patients with gastroesophageal reflux disease. Prior to the start of the study, endoscopy was performed in all patients that were then divided into two groups, depending on the presence or absence of reflux esophagitis. During the study, the patients were not allowed to take any medication which could affect the results of the study (sucralfate, misoprostol, H2-receptor inhibitors, other proton pump inhibitors, ketoconazole, itraconazole). They were allowed to take antacids if necessary.

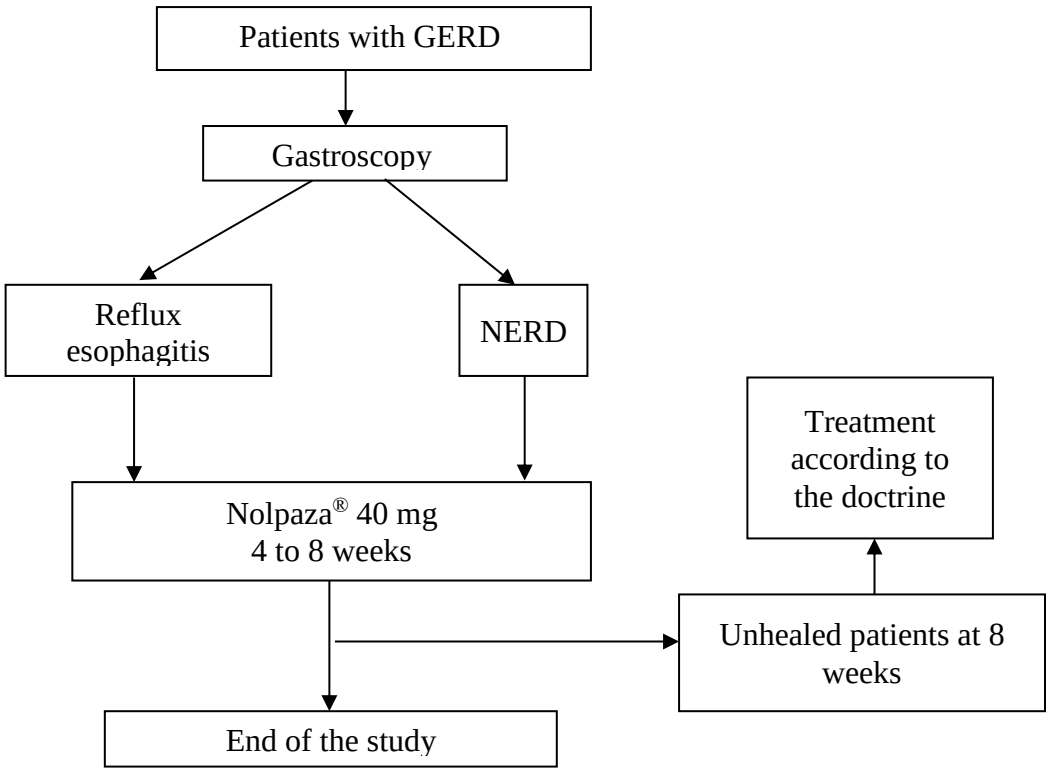

Figure 1 Scheme of the study

Sponsor:

- KRKA-POLSKA Sp. z o.o., Warszawa, ul. Równoległa 5, 02-235 Warszawa, Polska

Development phase of the study:
Phase IV

Name and affiliation of principal investigator:
Prof. dr hab. med. Andrzej Dąbrowski, Uniwersytecki Szpital Kliniczny in Białystok, Poland

Name of sponsor signatory:
Breda Barbič-Žagar, MD, Medical director, Krka, d. d., Novo mesto, Slovenia

MD Statement:
This study has been performed in compliance with the Good Clinical Practices (GCP/ ICH E 6).

Authors of the clinical study report:

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Date of the report:
November 2013

2. SYNOPSIS

Title	Efficacy and safety of **PAN**toprazole in the treatment and **S**ymp**T**om relief in patients with g**A**st**R**oesophageal reflux disease (GERD) – **PAN-STAR**
Protocol number	KCT 27/2009 – PAN-STAR/PL
Sponsor	KRKA-POLSKA Sp. z o.o., Warszawa, ul. Równoległa 5, 02-235 Warszawa, Polska
Methodology, Study design	Study was designed as multicenter, open labeled, prospective, phase IV study.
Study period	First patient enrolled in Poland: 17th July, 2012 Last patient enrolled in Poland: 6th December, 2012
Study centers	Study was carried out in 2 medical centers.
Objectives	Pantoprazole is effective in the relief of symptoms in GERD in most of the patients and there are no differences in its efficacy with regard to the presence of reflux esophagitis. The eradication of the symptoms of GERD depends on the duration of treatment. The treatment with pantoprazole 40 mg leads to a significant improvement of the quality of life of patients with GERD
Number of patients included in statistical analysis	Number of patients included in efficacy analysis: 100. Number of patients included into the safety analysis: 101.
Diagnosis	The study population consists of patients with gastroesophageal reflux disease.

Study product, dose, route, regimen	Gastroresistant tablets Nolpaza® in a dose of 40 mg. The tablets should not be chewed or crushed, and should be swallowed whole 1 hour before a meal with some water.
Duration of treatment	Patients were treated for 4 to 8 weeks.
Main inclusion criteria	• Patients of both genders at the age over 18 • Patients with typical GERD symptoms (heartburn or regurgitation), which are troublesome for the patient • Signed informed consent
Primary endpoint	• To establish the efficacy of the treatment with 40 mg of pantoprazole in patients with reflux esophagitis and in those with non-erosive reflux disease (NERD). • To establish the effect of the treatment duration on the healing of reflux esophagitis and non-erosive reflux disease (NERD).
Secondary endpoint	• To establish the effect of the treatment with pantoprazole 40 mg on the quality of life of patients with reflux esophagitis and in patients with non-erosive reflux disease (NERD.) • To quantify the rate of adverse events associated with pantoprazole treatment.
Study design	Study was performed in Poland. There were 3 visits during the study: ***Week 0 (Initial visit):*** - Patients meeting eligible criteria were allocated into two groups, depending on the presence or absence of reflux esophagitis: at the start of study course (Visit 1) patient were started the treatment with gastroresistant tablets Nolpaza® in a dose of 40 mg for 4 weeks. ***Week 4 (2nd visit):*** - <u>If patient fulfilled the healing criteria</u> (absence of the primary symptom, heartburn or regurgitation, during the last 7 days before the control visit/or its presence on not more than one day in the last week before the control visit, but in a mild form; no other symptom must be more marked than it was at the beginning of the treatment; i.e. must not be severe), **treatment with Nolpaza® 40 mg was stopped.** Visit for assessment of remission were planned after 4 weeks. - <u>If patient did not fulfill the healing criteria</u>, **treatment was continued with Nolpaza® 40 mg for next 4 weeks.** ***Week 8 (3rd visit):*** End of the study
Efficacy criteria for evaluation	• efficacy of the treatment with 40 mg of pantoprazole in patients with reflux esophagitis and in those with non-erosive reflux disease (NERD). • To establish the effect of the treatment duration on the healing of reflux esophagitis and non-erosive reflux disease (NERD). • To establish the effect of the treatment with pantoprazole 40 mg on the quality of life of patients with reflux esophagitis and in patients with non-erosive reflux disease (NERD.)

Criteria for safety evaluation	• Overall incidence of drug-related adverse events (adverse reactions) • Patients prematurely discontinuing the study due to adverse reactions, protocol violation and due to their decision to withdraw from the study were also included in the statistical analysis (in safety analysis).
Statistical methods	Upon conclusion of the study the investigators sent the Case Report Forms to KRKA where the statistical analysis and data processing were performed. The leading symptoms parameters are considered to be ratio scale random variables (at each visit). For analysis of the variables, the following descriptive statistics are presented: • The least and the largest values, • The average (arithmetic mean), • The (sample) standard deviation, • The standard error of mean. Because of the reasonably large sample, the asymptotic z-test is employed to assess the difference between means of two variables measured in the same population. Analogously, an asymptotic 95%-confidence interval for the difference between means is used for interval estimation. Microsoft Office Excel 2010© was used for the computational part of the analysis, and Microsoft Office Word 2010© was used to compile the report.
Efficacy results	The results show that Nolpaza® in a dose of 40 mg was found to be highly effective and safe in the treatment of GERD 17 % of patients met the healing criteria after 4 weeks of treatment and 54 % of patients after 8 weeks of treatment. Total symptom severity score in one patient was significantly reduced after 4 weeks of treatment. The average score was 3.02 assessed by 100 % of patients. Total symptom severity score in one patient was also significantly reduced after 8 weeks of treatment (including 40 % of patients in remission, who stopped treatment with Nolpaza® after 4 weeks of treatment). The average score after 8 weeks of treatment was 1.14, assessed by 99 % of patients. All patients receiving Nolpaza® for 4 weeks experienced an almost complete relief of leading symptoms assessed with an average score of 1.44 and 99 % of patients after 8 weeks of treatment with an average score of 0.48, together with a significant increase in the quality of life. Symptoms as heartburn, regurgitation, dysphagia, retrosternal pain, epigastric pain, eructation, nausea and cough were also significantly reduced during the study. In patients who fulfilled the healing criteria on the second visit (after 4 weeks of treatment), no significant increase in the severity of symptoms and no significant decrease in the quality of life were found 4 weeks after they discontinued therapy.
Safety results	Treatment with Nolpaza 40 mg was well tolerated, since 98 % of patients were without adverse events throughout the whole study. Investigators assessed that only 1 (1 %) patient experienced adverse reaction (allergic reactions) that was related to Nolpaza® treatment. This adverse reaction was assessed during 1st period. Due to severity and frequency of adverse reaction, patient discontinued treatment with Nolpaza after second visit.

Conclusion	The results of the present study show that Nolpaza® 40 mg was associated with completely relief of GERD related symptoms in majority of patients with GERD and NERD. Furthermore the severity of symptoms was significantly reduced in patients without complete relief of symptoms. This data suggest that Nolpaza 40 once daily might be an effective choice for providing symptom relief of patients with GERD. Furthermore, Nolpaza significantly improved the quality of life of treated patients.