1 Title Page

Clinical Study Report No. 459/2007

Version 1.0

Title: Treatment response in patients with symptoms due to gastroesophageal reflux disease either with or without esophagitis treated with Pantoprazole sodium 40 mg o.d. over 8 weeks	Version date: 04-Dez-2008 INN: Pantoprazole sodium Project No./List No.: BY1023 Compound No.: B8610-023 Batch No.: 00000851, 00000852, 00000853
Study Protocol No.: **BY1023/M3-341**	Development phase: III
EudraCT No: 2005-003485-42	Indication studied: Gastroesophageal Reflux Disease (GERD)
Study initiation date:09-May-2006 (first patient in)	Date of early termination: not applicable
Study completion date:14-Aug-2007 (hard-lock of the database)	Summary of modifications: not applicable

Name and country of investigators:

Multicenter study: 167 centers in Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hong Kong, India, Italy, Malaysia, Mexico, Poland, Portugal, Singapore, South Africa, South Korea, Spain, Switzerland, Taiwan, United Kingdom.

Coordinating investigator:

Text redacted to protect personally identifiable information

Name of sponsor's responsible medical officer:

[redacted] Nycomed GmbH, Byk-Gulden-Strasse 2, 78467 Konstanz, Germany

Person(s) responsible for study report:

[redacted] Nycomed GmbH, Byk-Gulden-Strasse 2, 78467 Konstanz, Germany

Sponsors contact persons:

See accompanying letter of the regulatory approval application

Statement of GCP compliance:

This study was performed in accordance with Good Clinical Practice regulations as set forth in the ICH Consolidated Guideline E6 (CPMP/ICH/135/95)

Archiving responsibility for essential documents:

Department RCO/G2 at Nycomed GmbH, local sponsor (if applicable) and investigator according to ICH Consolidated Guideline E6.

2 Synopsis

Title of the study:

Treatment response in patients with symptoms due to gastroesophageal reflux disease either with or without esophagitis treated with Pantoprazole sodium 40 mg o.d. over 8 weeks.

Principal Investigator(s) and study center(s):

The study was a multicenter study and conducted by 167 investigational sites in Argentina, Australia, Austria, Belgium, Brazil, Canada, France, Germany, Hong Kong, India, Italy, Malaysia, Mexico, Poland, Portugal, Singapore, South Africa, South Korea, Spain, Switzerland, Taiwan, and United Kingdom.

Coordinating investigator(s):

[redacted] Friesenstrasse 27, 71640 Ludwigsburg, Germany

Publication (reference):

- Monnikes H, Schmitt H, Berghoefer P, Doerfler H, Heading R. Physicians Underestimate Symptom Burden and Overestimate Treatment Effects in GERD Patients. Gastroenterology 2008, 134, 4 Supplement 1: A-173
- Heading R, Berghoefer P, Doerfler H, Schmitt H, Monnikes H. Interactions of GERD-Related Symptoms, Health-Related Quality of Life and Anxiety and Depression in GERD Patients Treated with a PPI. Gastroenterology 2008, 134, 4 Supplement 1: A-323
- Heading RC, Berghöfer P, Dörfler H, Schmitt H, Mönnikes H. Inter-Relationship of Gastrointestinal Symptoms, Health Related Quality of Life and Depression and Anxiety in GERD Patients on PPI Therapy. Gut 2008; 57 (Suppl II): A 101
- Mönnikes H, Schmitt H, Berghöfer P, Dörfler H, Heading RC. A Discrepancy between Patient-assessed Treatment Satisfaction and Physician Assessment of Symptom Relief in GERD. Gut 2008; 57 (Suppl II): A 100
- Heading R, Doerfler H, Berghoefer P, Schmitt H, Monnikes H. Pre-Treatment Request™ Scores Can Predict Response to PPI Therapy in GERD Patients. Gastroenterology 2008, 134, 4 Supplement 1: A-177
- Heading RC, Dörfler H, Berghöfer P, Schmitt H, Mönnikes H. Prediction of Response to PPI Therapy in GERD Patients Using Pre-Treatment REQUEST Scores. Gut 2008; 57 (Suppl II): A 100

Studied period:

09-May-2006 (first patient in) to 14-Aug-2007(hard-lock of the database)

Clinical phase:

Phase III

Objectives:

Identification of factors determining response to treatment with Pantoprazole 40 mg o.d. as measured by different methods

Methodology:

- open, multinational, multicenter study
- study period per patient: 8 weeks treatment with Pantoprazole 40 mg o.d, three visits were performed: visit 0 (V0), visit 1 (V1) and visit 2 (V2 =V_{end}).

No. of patients (total and for each stratum) planned and analyzed:

- 2000 FAS (full analysis set) patients and 1600 VCS (valid cases set) patients were planned to be included into the study.
- analyzed sets:

GERD grade	Enrolled	Safety set	Full analysis set	Valid cases set
Missing	13	13	13	11
Normal	713	700	694	566
GERD A	690	685	680	557
GERD B	389	383	381	327
GERD C	99	97	97	72
GERD D	24	23	23	16
Total	1928	1901	1888	1549

Diagnosis and main criteria for inclusion:

- written informed consent by the patient for study participation, prior to protocol specific procedures;
- outpatients of at least 18 years of age (21 years in Argentina);
- patient considered by the investigator to have symptoms due to gastroesophageal reflux disease (GERD);
- patients whose compliance was expected to be high with respect to the completion of the questionnaires and diaries (ReQuest™ (Reflux Questionnaire), GERDyzer™ (GERD Analyzer), HADS (Hospital Anxiety and Depression Scale), TSS (Treatment Satisfaction Sheet)) according to the assessment of the investigator.

Test product, dose, mode of administration, batch no.:

Pantoprazole-Na 40 mg (enteric coated tablets) once daily, oral, 00000851, 00000852, 00000853

Reference product, dose, mode of administration, batch no.:

Not applicable

Duration of treatment:

8 weeks per patient

Criteria for evaluation:

Primary variable:

The primary variable of efficacy is the response to treatment[1] with Pantoprazole 40 mg o.d. at week 8 as measured by ReQuest™-GI in relation to various response factors as measured by ReOuest™ and its subscales. A patient is considered a responder at visit 2, if the symptom score as measured by the subscale 'GI' (ReQuest™-Gastrointestinal) of the ReQuest™ is below the pre-defined GERD symptoms threshold of 1.6 on all of the 3 consecutive days prior to visit 2.

Secondary variables:

- The response to treatment with Pantoprazole 40 mg o.d. at week 4 as measured by ReQuest™-GI in relation to various response factors as measured by ReQuest™ (total score, GI score, WSO score, and possible pre-post differences within the first ten days of ReOuest™), analyzed analogously to the primary analysis;
- The treatment satisfaction after 4 and 8 weeks of treatment as measured by patient assessment (TSS), analyzed using descriptive methods;

[1] According to a File Note dated 27-Sep-2008 to Section 11.2.1 of the final SAP, the following modification was established:

Differing from the SAP, a patient was considered a responder at visit 2, if the symptom score as measured by the subscale 'GI' of the ReQuest™ was below the pre-defined GERD symptoms threshold on the last three existing consecutive days, considering the accepted range for visit date differences and no 'GI-score' above this threshold occurred for a single day after the three days period. The change was based on the reflection that a range of 49 to 63 days was accepted for the visit date differences, so that for the analysis of the last three consecutive days prior to visit 2 a range of days between day 46 and 59 was considered, depending on the date of visit 2 of a patient. Since the data documented at visit 2 were not part of the primary criterion, it was reasonable to allow the range of 46 to 59 days for the three last existing consecutive days dependent on the accepted visit date range, if no GI score above the pre-defined GERD symptoms threshold afterwards (between three days and Vend).The same procedure was applied for the definition of a responder at V1.

- The control of reflux symptoms at baseline and after 4 and 8 weeks of treatment as measured by investigator assessment, analyzed using descriptive methods.
- Treatment satisfaction as measured by patient assessment (TSS), the control of reflux symptoms measured by investigators assessment, and the response to treatment after 4 and 8 weeks, analyzed using the Spearman correlation coefficient;
- For analysis of the association of responders/non-responders with esophagitis, the responder rates and the corresponding exact two-sided 95% confidence intervals were calculated separately for patients with and without erosive esophagitis assessed at baseline. In addition, the variable erosive/non-erosive GERD was included as an additional factor in the regression model (1) and was analyzed analogously to the primary variable.
- For analysis of the association of responders/non-responders with the HADS score, descriptive statistics were calculated for the HADS score separately for responders and non-responders.
- For analysis of the association of responders/non-responders with the investigator's judgment of IBS (Irritable bowel syndrome) symptoms, the responder rates and the corresponding exact two-sided 95% confidence intervals were calculated for patients with or without IBS symptoms as judged by the investigator;
- The HRQoL (Health related Quality of Life) as measured by GERDyzer™, analyzed using descriptive methods;
- For analysis of the association of responders/non-responders with serological *H. pylori* (*Helicobacter pylori*) status, the responder rates and the corresponding exact two-sided 95% confidence intervals was calculated for each *H. pylori*-status at baseline.
- The time to reach first symptom relief, based on the pre-defined GERD symptoms threshold of the ReQuest™-GI, analyzed using Kaplan-Meier methods. A patient was defined to be relieved of symptoms the first time, if the symptom score as measured by the subscale 'GI' of the ReQuest™ fell below the pre-defined GERD symptoms threshold of 1.6 on three consecutive days for the first time;
- The time to reach sustained symptom relief that is based on the pre-defined GERD symptoms threshold of the ReQuest™-GI, analyzed using Kaplan-Meier methods.

Statistical methods:

Efficacy

- primary analysis based on the ITT population is the response to treatment with Pantoprazole 40 mg o.d. at week 8 as measured by ReQuest™-GI in relation to various response factors as measured by ReQuest™ and its subscales. Calculation of the responder rate and the respective 95% CI (confidence interval).

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

Demographic and other baseline characteristics

Demographic variable		FAS N = 1888	VCS N = 1549
Age [years]	Median (range)	47.09 (18.1, 91.9)	46.92 (18.1, 84.5)
Height [cm]	Mean ± SD	167.5 ± 9.57	167.6 ± 9.60
Weight [kg]	Mean ± SD	74.2 ± 15.82	74.6 ± 15.98
BMI [kg/m²]	Mean ± SD	26.39 ± 4.81	26.48 ± 4.86
Race [N]	Asian	352 (18.6)	286 (18.5)
	Black	43 (2.3)	33 (2.1)
	White	1326 (70.2)	1086 (70.1)
	Other	167 (8.8)	144 (9.3)
Gender [N]	Male	910 (48.2)	764 (49.3)
	Female	978 (51.8)	785 (50.7)
Smoking [N]	Never	1179 (62.4)	981 (63.3)
	Former	360 (19.1)	283 (18.3)
	Current	349 (18.5)	285 (18.4)

N = number of patients, SD = standard deviation, FAS = full analysis set, VCS = valid cases set.

Study results

Efficacy results

The response to treatment with Pantoprazole 40 mg o.d. at week 8 as measured by ReQuest™-GI in relation to various response factors as measured by ReQuest™ and its subscales was analyzed as the primary variable of this study. After 8 weeks of treatment the response rate was 72.6% [95% CI = 70.3; 74.9] for patients of the valid cases set. It was assumed that the response or non-response to treatment could be predicted at the early time point or time interval using the "predictive value". As predictive key values with either good prediction for response or non-response ReQuest™ total score, ReQuest™-GI score and ReQuest™-WSO (well-being, sleep disturbances and other complaints) score as well as different possible pre-post differences of each of the three ReQuest™ scores were investigated. The study demonstrated that the best time point for prediction of response to treatment with Pantoprazole 40 mg after 8 weeks was day 10 for ReQuest™-GI subscale. At this time point the highest prediction rate for response, which was 88.0% and non-response,

which was 68.3%, were observed and the related highest lower and upper exact confidence intervals for both response [95% CI = 85.7; 90.1] and non-response [95% CI = 60.0; 75.9] were determined. For ReQuest™-WSO subscale the highest prediction rates for response and non-response were calculated for day 4 and for ReQuest™-total score for day 1 of treatment.

For pre-post differences the best prediction of response to treatment with Pantoprazole 40 mg after 8 weeks was shown for ReQuest™ total score for the difference: day 9 – day 1. For this time interval the highest prediction rates for response and non-response, 76.6% and 55.5%, respectively were observed. Furthermore, the highest lower and upper exact confidence intervals for both response [95% CI = 74.2; 78.9] and non-response [95% CI = 48.0; 62.8] were shown.

To investigate the quality of the identified predictive key values the influence of different days of treatment on response at 8 weeks was investigated. The greatest influence on response to treatment at week 8 was shown for ReQuest™-GI score on day 10. R-Square values of the logistic regression model I and II were 0.1650 and 0.1394, respectively. The influence was statistically significant as the p-values (Wald test) were below 0.0001 for both models. The influence of predictive key value ReQuest™ total score for day 9 – day 1 on the response to treatment was not statistically significant as all p-value (Wald test) was above 0.0001 for model II.

Overall, it is possible basing on the ReQuest™ total score and its subscales to predict the response or non-response of the patient to the treatment at early time point/interval (days 1-10). The best prediction of response to treatment after 8 weeks was shown for ReQuest™-GI subscale for day 10.

The response to treatment with Pantoprazole 40 mg o.d. at week 4 was analyzed. The response rate was 60.6% [95% CI = 58.1; 63.0] for patients of the valid cases set. The highest prediction rates for response and non-response at week 4 of treatment were observed for ReQuest™-total score and for ReQuest™-GI score for day 7 and for ReQuest™-WSO for day 1. The predictions of ReQuest™ total score and of ReQuest™-GI subscale were better than ReQuest™-WSO subscale regarding response and non-response.

The influence of predictive key values on treatment response at week 4 was analyzed. For both ReQuest™-total score and ReQuest™-GI score for day 7 the influence was comparable and in both cases greater than the influence of ReQuest™-WSO score on day 1. R-Square values of the logistic regression model I and II for ReQuest™-GI were 0.2629 and 0.2520, respectively and for ReQuest™-total score: 0.2457 and 0.2635, respectively. The influence of all key predictive values (ReQuest™ total score on day 7, ReQuest™-GI score on day 7 and ReQuest™-WSO score on day 1) on the response to treatment with Pantoprazole was statistically significant (p-values < 0.0001 for both models, Wald test).

For pre-post differences the best prediction of response to treatment with Pantoprazole 40 mg after 4 weeks was shown for pre-post difference day 5 – day 3 for ReQuest™-GI, for day 9 - day 4 for ReQuest™-total score and for day 6 – day 1 for ReQuest™-WSO score. The influence of predictive key values on response to treatment was analyzed. For ReQuest™

total score for day 9 – 4 and ReQuest™-GI score for day 5 – 3 the influence on response to treatment was not statistically significant (Wald test: p-values > 0.0001 for model II). Only the influence of ReQuest™-WSO score for day 6 – day 1 was statistically significant (Wald test: p-values < 0.0001 for both models).

Overall, the best prediction of response to treatment after 4 weeks was shown for day 7 for ReQuest™-total score and for ReQuest™-GI subscale.

An increase in treatment satisfaction of the patients from week 4 to week 8 was observed.

The treatment satisfaction was measured after 4 and 8 weeks of treatment. 52.4% of patients from the valid cases set were very satisfied with the management of their GERD symptoms after 4 weeks and 63.8% after 8 weeks. Only 4.8% of patients from the valid cases set were not satisfied after 4 weeks and the percentage decreased to 3.7% after 8 weeks.

At baseline for 3.6% of patients from the valid cases set the investigator assessed reflux symptoms as "well controlled", after 4 weeks of treatment with Pantoprazole 40 mg the percentage increased to 69.3% of patients and after 8 weeks to 82.1%. The percentage of patients from the valid cases set who could not control the symptoms of reflux according to the investigator decreased with the time.

The correlation between the items "control of reflux symptoms" - "response to treatment" and "response to treatment" - "treatment satisfaction" was calculated. Spearman correlation coefficient of -0.33 was shown for "control of reflux symptoms" and "response to treatment" after 4 weeks and for "treatment satisfaction" and "response to treatment" after 4 weeks correlation coefficient of -0.39 was observed. For week 8 the correlation coefficient for parameters "control of reflux symptoms" and "response to treatment" was -0.37 and for "treatment satisfaction" and "response to treatment" was -0.45. Overall, no high correlation between the items was observed.

The observed response rates for patients with GERD were higher than for patients with enGERD. A response rate of 76.9% [95% CI = 74.1; 79.5] was calculated for 951 patients with GERD-Grade A to D after 8 weeks of treatment. For patients with enGERD a response rate of 66.1% [95% CI = 61.9; 70.0] was calculated.

The possible differences between Pantoprazole responders and non-responders with regard to psychological constitution were analyzed using HADS score and GERDyzer™ score. For patients who positively responded to treatment after 8 weeks the mean score of HADS at day 1 was 13.3 (SD: 7.18) and for non-responders: 16.8 (SD: 7.13). At the end of treatment the mean HADS score 8.6 (SD: 6.27) was calculated for responders and 14.1 (SD: 7.43) for non-responders. The results show that already at baseline the mean HADS score for responders was lower than for non-responders. Similar tendency was observed for GERDyzer™. For responders the mean total score of 32.21 (SD: 16.608) was calculated on day 1 and for non-responders the mean total score amounted 40.03 (SD: 14.519). The total score for both groups continued to increase and reached at the end of treatment for responders 6.04 (SD: 6.895) and for non-responders 21.53 (SD: 13.484).

The response rate for patients who suffered from the IBS was 63.1% [95% CI = 56.2, 69.6] and was lower than for patients who did not suffer from the IBS and for whom the calculated response rate was 74.1% [95% CI = 71.6, 76.6].

There was no considerable difference in response rates between *H. pylori* positive and *H. pylori* negative patients.

The mean time to reach first symptom relief for the valid cases set was 17.3 days (SE: 0.4795). 25% of patients from the valid cases set reached the first symptom relief after 4 days of treatment. After 8 days [95% CI = 7.0; 8.0] of treatment 50% of patients reached the first symptom relief and 75% of patients after 24 days [95% CI = 21.0; 27.0] of treatment. The mean time to reach sustained symptom relief days for the valid cases set was 36.2 (SE (standard error): 0.5424). For 25% of patients the time to reach sustained symptom relief fell on day 14 [95% CI = 12.0; 17.0]. 50% of patients reached the sustained symptom relief after 42 days [95% CI = 40.0; 44.0] and 75% of patients after 59 days (the end of treatment).

Safety results

Treatment-emergent adverse event (TEAEs) (safety set, N = 1901)

	Number	%
Number of patients with TEAEs	477	25.1[a]
Number of TEAEs (according to MedDRA Code)	784	-
Number of patients with SAEs	14	0.7[a]
Deaths	-	-
TEAEs with causality suggested as 'likely' by the investigator	151	19.3[b]
TEAEs with causality suggested as 'definitely' by the investigator	2	0.3[b]
Number of patients with TEAEs leading to the premature discontinuation	46	2.4[a]

[a] Percentages are based on the total number of patients in the safety set
[b] Percentages are based on the total number of TEAEs
TEAE = treatment-emergent adverse event, N = number of patients with events, SAE = serious adverse event

No patient died in the course of the study. In total, 16 treatment emergent serious adverse event symptoms occurred in 14 patients (0.7%) of the safety set during the study period. The investigators assessed 14 treatment emergent SAEs (serious adverse events) as 'unrelated' and 2 as 'unlikely related' to study medication intake.

Overall, 25.1% of all patients in this study experienced a TEAE (treatment emergent adverse event) (477 patients out of 1901 patients).

The most often reported adverse events as coded by the medical dictionary for regulatory activities (MedDRA) were 'headache', 'diarrhoea', 'nausea', 'abdominal pain', 'constipation' and 'influenza'. Other adverse events occurred in less than 1% of patients.

The majority of treatment-emergent adverse events were of mild (56.9%) and moderate (37.9%) intensity. The investigators reported a severe intensity only for 5.2% of all TEAEs.

For 46 patients (2.4%) TEAEs led to premature discontinuation. Out of these, 1 was assessed as 'definitely' and 27 as 'likely related' to the intake of study medication by the investigator, while the sponsor assessed 3 of the events as 'definitely' and 27 as 'likely related' to the intake of study medication. In the case of five patients with SAEs which led to premature discontinuation, one ('ischaemic stroke') was assessed by the investigator as unlikely related to the study medication intake and by the sponsor as unrelated, in four other cases the investigators and the sponsor agreed that there was no relation to the study medication intake.

One female patient terminated the study due to a positive pregnancy result at visit 1 (V1). The patient refused to provide any further data concerning her pregnancy. At the time of reporting, she did not intend to deliver the baby. No further information was provided to the sponsor. This coincidental event had no influence on the risk/benefit evaluation of Pantoprazole.

In conclusion, Pantoprazole was well tolerated and safe.

Conclusions:

The objective of the study was investigation of factors determining the response to treatment with Pantoprazole 40 mg o.d. using different methods of measurement eg ReQuest™ questionnaire, patient and investigator assessment.

The study demonstrates that the prediction of response or non-responders at week 8 can be made after only 10 days of the Pantoprazole treatment. The best prediction of the response to treatment after 8 weeks was shown for ReQuest™-GI subscale.

The influence of several factors on the response to treatment was confirmed. Patients suffering from GERD had a better response rate to Pantoprazole treatment than patients with enGERD. In patients suffering from irritable bowel syndrome (IBS) the response rate was lower than in non-IBS patients. Patients responding to treatment with Pantoprazole had a lower HADS total score and lower score of GERDyzer™ at baseline.

For other factors, for example the *H. pylori* status of patients no influence on the response rate was shown.

Overall, using of ReQuest™ questionnaire a differentiation between responders and non-responders can be made already after few days of the therapy.

The study medication Pantoprazole was well tolerated and safe. No patient died during the course of this study. All 16 treatment emergent serious adverse events which occurred in 14 patients of the safety set were assessed as 'unrelated' (14) or as 'unlikely related' (2) to study medication intake.

Date of report: {04-Dez-2008}