1 Title Page Clinical Study Report No. 207/2007 Version 1.0

Title: **»COMPETITION«** Investigation of clinical endpoints for treatment-induced gastroesophageal reflux disease (GERD) symptom changes	Version date: 10 July 2008 INN: Pantoprazole Project No. / List No.: BY1023 Compound No.: B8610-023 Batch No.: Austria, Germany, Hungary: 00300801 Australia: 00300802
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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)	
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2 Synopsis

Title of the study:

» COMPETITION «:

Investigation of clinical endpoints for treatment-induced gastroesophageal reflux disease (GERD) symptom changes

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

[redacted] M.D., 'Leiter der Klinischen Prüfung' according to German Drug Law, Klosterstraße 7, 23858 Reinfeld, Germany.

The study was conducted in 37 centers in Australia, Austria, Germany, and Hungary.

Coordinating investigator(s) (if applicable):

[redacted], M.D., Department of Gastroenterology, Hepatology and General Medicine, Royal Adelaide Hospital, North Terrace, Adelaide SA 5000, Australia

Publication (reference):

- Holtmann G, Hunt R, Katelaris P, Berghoefer P, Doerfler H, Tack J (2007): What is the truth? Sleep disturbance as assessed by investigators or a validated instrument (ReQuest™) in patients with Gastro-Esophageal Reflux Disease (GERD). Gut 56 (Suppl. III):A214
- Holtmann G, Hunt R, Tack J, Korell A, Doerfler H, Katelaris P (2007): Symptom relief assessed by ReQuest™: a superior clinical endpoint compared to investigator-assessed heartburn? Gut 2007; 56 (Suppl III):A215

Studied period:

July 2006 – March 2007 (Study start was defined as first patient in, study end was defined as the hard-lock of the database)

Planned recruitment period:

03 July 2006 – 25 September 2006

First patient in: July 2006, Last patient out: January 2007

Clinical phase: III

Objectives:

The objective of the present study was to investigate the validity of two different clinical endpoints for treatment-induced GERD symptom changes, i.e., investigator-assessed heartburn versus symptom assessment by a patient self-assessed validated GERD symptom questionnaire (ReQuest™), in terms of its psychometric characteristics and sensitivity/specificity.

Methodology:

Study design:

The study was designed as an open, multinational, multicenter study. Recruitment was non-competitive. Only in case that during the scheduled recruitment phase it became obvious that the enrollment of 660 patients would not be achieved, the recruitment strategy was switched to a competitive mode irrespective of time and certain country quotas.

Study period per patient:

The study period per patient comprised totally 36 days; 8 days pre-treatment followed by 28 days treatment with o.d. pantoprazole 40 mg.

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

Outpatients of both genders of at least 18 years of age with gastroesophageal reflux esophagitis (erosive GERD) or endoscopic-negative GERD (enGERD). All patients had to suffer from symptoms before inclusion into the study as well as during the pre-treatment phase.

Planned sample size

660 patients were planned to be enrolled into the study, 560 patients were planned to be available for the full analysis set, and 423 patients were planned to be available for the per-protocol (PP) set.

Analyzed sets:

A total of 694 patients was enrolled into the study. 651 patients received study medication during the treatment phase, thus the safety set comprised 651 patients. All of them were treated with pantoprazole 40 mg o.d. 18 patients of the full analysis set were excluded from the full analysis set as they were not eligible, so that the full analysis set comprised 633 patients. 95 patients were excluded from the per-protocol set, either due to baseline findings

in lab values that led to exclusion as predefined in the protocol, or because of major deviations from the study protocol. As a consequence, the per-protocol set comprised 538 patients.

Diagnosis and main criteria for inclusion:

- written informed consent by the patient for study participation, prior to protocol specific procedures;
- patients of at least 18 years of age;
- history of GERD-related symptoms for at least 6 months prior to inclusion into the study;
- heartburn (defined as a burning feeling, rising from the stomach or lower part of the chest up towards the neck) on at least 3 days during the last week prior to inclusion into the study as assessed by the investigator;
- acid complaints on at least 3 days during the last week prior to inclusion into the study as assessed by the investigator;
- endoscopically confirmed gastroesophageal reflux esophagitis (Grade A to D classification determined via the Los Angeles classification system) or symptom based diagnosis of endoscopic-negative GERD (enGERD);
- patients whose compliance was expected to be high with respect to the completion of ReQuest™ and GERDyzer™ according to the assessment of the investigator.

Interim Exclusion Criteria

The following interim exclusion criteria were evaluated after the pre-treatment period (8 days).

Patients meeting any of the following criteria were excluded:

- patients who did not suffer from at least 5 episodes of acid complaints within the pre-treatment period as documented in ReQuest™ by the patients;
- development of any of the exclusion criteria as outlined above.

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

The patients were treated with o.d. pantoprazole 40 mg (pantoprazole sodium sesquihydrate, enteric-coated tablets) over 28 days. The patient had to take o.d. 1 tablet pantoprazole 40 mg with water 1 hour before breakfast. Tablets should not have been chewed or crushed and had to be swallowed whole before breakfast with water.

Batch no.: Austria, Germany and Hungary: 00300801

Australia: 00300802

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

Not applicable.

Duration of treatment:

The duration per patient was 8 days pre-treatment period and 28 days treatment period.

Criteria for evaluation:

Primary variable

The primary variable of the study was the misclassification rate as defined below.

For each patient the following two assessments were made:

- Investigator-assessed heartburn;
- Symptom assessment by ReQuest™-GI.

A patient was defined as misclassified if one of the following two statements was true:

- The patient is below the predefined ReQuest™–GI GERD symptom threshold (i.e., 1.60 based on the 95% percentile, Stanghellini et al., 2006) on all of the 3 consecutive days prior to day 14 and is not heartburn free (investigator-assessed) on at least one of the 7 consecutive days prior to day 14.
- The patient is above the predefined ReQuest™–GI GERD symptom threshold on at least one of the 3 consecutive days prior to day 14 and is heartburn free (investigator-assessed) on all of the 7 consecutive days prior to day 14.

Secondary variables

- the rate of patients below the predefined ReQuest™-GI GERD symptom threshold on all of the 3 consecutive days prior to day 28 will be compared with the rate of patients who are heartburn free (investigator-assessed) on all of the 7 consecutive days prior to day 28.

- the rates of patients below the predefined ReQuest™-GI GERD symptom threshold on all of the 3 consecutive days prior to day 7, 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- the rates of patients who are free from acid complaints measured by ReQuest™-GI on all of the 3 consecutive days prior to day 7, 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- the rates of patients who are heartburn free (investigator-assessed) on all of the 7 consecutive days prior to day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- the rates of patients who are free from acid complaints measured by ReQuest™-GI on all of the 7 consecutive days prior to day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- the rates of patients who are free from acid complaints (investigator-assessed) on all of the 7 consecutive days prior to day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- the rates of patients who are free from acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints and nausea measured by ReQuest™-GI on all of the 7 consecutive days prior to day 14 and 28 and the corresponding exact two sided 95% confidence intervals will be calculated.
- the rates of patients who are free from acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints and nausea (investigator-assessed) on all of the 7 consecutive days prior to day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- the rates of patients who are free from sleep disturbances measured by ReQuest™-WSO on all of the 7 consecutive days prior to day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- the rates of patients who are free from sleep disturbances (investigator-assessed) on all of the 7 consecutive days prior to day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- sensitivity and specificity of ReQuest™-GI based on Patient's Global Question on day 7, 14, and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- sensitivity and specificity of acid complaints measured by ReQuest™-GI based on Patient's Global Question on day 7, 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.

- sensitivity and specificity of heartburn (investigator-assessed) based on Patient's Global Question on day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- sensitivity and specificity of acid complaints, upper abdominal/stomach complaints, lower abdominal/digestive complaints and nausea (investigator-assessed) based on Patient's Global Question on day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated.
- sensitivity and specificity of investigator's assessment based on Patient's Global Question on day 14 and 28 and the corresponding exact two-sided 95% confidence intervals will be calculated. To analyze the influence of severity of erosive GERD (LA grade A-D) and enGERD on the primary variable, all calculated sensitivities, specificities and the Receiver Operating Characteristics; these parameters will be analyzed for each GERD status at baseline.
- to analyze the influence of severity of *H. pylori* status on the primary variable, all calculated sensitivities, specificities and the Receiver Operating Characteristics; these parameters will be analyzed for each *H. pylori* status at baseline.
- test-retest reliability of heartburn (investigator-assessed) measured on day –7 and day 0 will be determined.
- test-retest reliability of heartburn (patient-assessed) measured on day –7 and day 0 will be determined.
- the Receiver Operating Characteristics of ReQuest™, ReQuest™-GI, ReQuest™-WSO, acid complaints, heartburn and investigator assessment using Patient's Global Question as external anchor will be determined.
- the endoscopic healing rates after 28 days of treatment with pantoprazole 40 mg once daily will be compared between the subgroups of patients with different combinations of the results from the two assessment methods (i.e. above below or not below the predefined ReQuest™-GI GERD symptom threshold on all of the 3 consecutive days prior to day 14 and free or not free from investigator-assessed heartburn on all of the 7 consecutive days prior to day 14).
- the endoscopic healing rates after 28 days of treatment with pantoprazole 40 mg once daily will be compared between the subgroups of patients with different combinations of the results from the two assessment methods (i.e. above below or not below the predefined ReQuest™-GI GERD symptom threshold on all of the 3 consecutive days prior to day 28 and free or not free from investigator-assessed heartburn on all of the 7 consecutive days prior to day 28).
- the health-related quality of life after 28 days of treatment with pantoprazole 40 mg once daily will be compared between the subgroups of patients with different combinations of the results from the two assessment methods (i.e. above below or not

below the predefined ReQuest™-GI GERD symptom threshold on all of the 3 consecutive days prior to day 14 and free or not free from investigator-assessed heartburn on all of the 7 consecutive days prior to day 14).

- the health-related quality of life after 28 days of treatment with pantoprazole 40 mg once daily will be compared between the subgroups of patients with different combinations of the results from the two assessment methods (i.e. above below or not below the predefined ReQuest™-GI GERD symptom threshold on all of the 3 consecutive days prior to day 28 and free or not free from investigator-assessed heartburn on all of the 7 consecutive days prior to day 28).
- safety

Changes made concerning the evaluation criteria are described in Section 9.8.

Statistical methods:

The two-sided 97.5% confidence interval for the misclassification rate was calculated. If the two-sided 97.5% confidence interval for the misclassification rate lay entirely above 10% a clinically relevant and significant difference of the assessment methods could be concluded. This procedure corresponded to a two-sided test on an α-level of 2.5%.

The following hypothesis will be tested for the primary variable of the study, i. e. the misclassification rate as defined in chapter 11.2.1:

$$H0: \pi \leq 10\% \quad \text{vs.} \quad H1: \pi > 10\%$$

whereby π denotes the misclassification rate.

The misclassification rate was assumed to be 30% on day 14. The precision of this estimation should be 5% for the 97.5% confidence interval. A total of 423 patients have to be available for the PP set on which the analysis of the primary variable will be based.

Withdrawn patients will not be replaced.

SUMMARY - CONCLUSIONS

Demography and baseline characteristics

The demographic data of the full analysis set were raised as follows:

- gender: 304 patients (48.0%) were male, 329 subjects (52.0%) were female, resulting in an approximately equal distribution of gender overall;

- age: ranged from 18 to 87 years with a mean of 51.59 years;
- height: ranged from 150.0 to 198.0 cm with a mean of 170.38 cm;
- weight: ranged from 40.0 to 140.0 kg with a mean of 77.61 kg;
- BMI: ranged from 15.82 to 57.69 kg/m² with a mean of 26.69 kg/m².

404 patients (63.8%) never smoked, 79 patients (12.5%) were former smokers and 150 patients (23,7%) were current smokers.

Study results

Efficacy

The primary variable was the misclassification rate derived from comparison of the self-assessment of GERD symptoms by patients via ReQuest™-GI and investigator-assessed heartburn prior to day 14 of the treatment period. In the PP set, a misclassification rate of 38.4% (CI [33.7%, 43.2%]) was calculated, showing a high discrepancy, and thus a clinically relevant and significant difference between patients' and investigators' assessment, as the two-sided 97.5% confidence interval lay entirely above the predefined 10% threshold. The efficacy variable misclassification rate prior to day 28 also showed a clinically relevant and significant difference between patients' and investigators' assessment. Here, the result was 29.4% (CI [24.8%, 34.4%]).

Regarding the rates of patients, an obvious numerical difference between patient and investigator assessment existed.

The calculation of sensitivity and specificity of secondary variables both showed an obvious numerical difference between patients' assessment and investigators' assessment.

Overall, the sensitivity was higher for the assessment of symptoms by patients via ReQuest™-GI. Values lay mostly higher than 65%. In some subgroup analyses sensitivity was lower due to low patient numbers in the respective subgroups. Specificity of ReQuest™-GI generally showed values higher than 65%, too.

Values for sensitivity of investigator assessment generally were lower than for patients' assessment. Especially for day 14 they were mostly lower than 50%. The specificity of investigator assessment was high. Most values were above 75%.

Also the test-retest reliability of patient-assessed heartburn showed better results than the investigator assessment. For patient assessment, the ICC was 0.9, indicating a very good test-retest reliability, whereas for investigator assessment the ICC was –8.0.

The graphs of the ROCs showed in general, that sensitivity was high for low values of 1-specificity. This indicates a high number of correctly classified patients even at low values for 1-specificity.

Overall, the results indicate that the ReQuest™-GI is an accurate and sensitive tool for the assessment of GERD related symptoms by patients. The numerical differences between patient and investigator assessment suggest, that patient assessment is more sensitive than assessment done by the investigator.

Safety

No serious adverse events (SAEs) occurred in the safety set during the study. In total, 8.0% of the patients in this study experienced a treatment emergent adverse event (AE) and 71 adverse events were reported in 52 out of 651 patients.

The most often reported adverse events as coded by the medical dictionary for regulatory activities (MedDRA) were 'headache', 'diarrhoea', and 'dry mouth'. Other adverse events occurred with a frequency of ≤ 2 symptoms.

The majority of treatment emergent adverse events was of 'mild' (74.6%) and 'moderate' (23.9%) intensity. Only for one symptom (1.4% of all AEs) a 'severe' intensity was reported by the investigator.

Three patients prematurely discontinued the study because of an adverse event. One of these AEs was assessed as 'likely' related to the intake of study medication by the investigator ('unlikely' by the sponsor).

No patient died during the course of this study.

In the measurement of vital signs performed at the end of treatment, none of the parameters assessed showed systematic or relevant changes during the course of the study.

In conclusion, pantoprazole was well tolerated and safe.

Conclusions:

In summary, pantoprazole was well tolerated and safe in the treatment of GERD. The results show that the ReQuest™-GI is a very accurate and very sensitive tool for the assessment of GERD related symptoms by patients. The numerical differences between patient and investigator assessment suggest, that patient assessment is more sensitive than assessment done by the investigator. Additionally, it is self-evident, that two factors influence the investigator assessment: first, patients apparently do not report their symptoms correctly to the physician. Secondly, physicians might underestimate the severity of symptoms of their patients.

Date of report: July 10, 2008