SYNOPSIS

Issue Date: 23 March 2012

Name of Sponsor/Company	Janssen-Cilag International NV
Name of Finished Product	Not applicable
Name of Active Ingredient(s)	Not Applicable

Protocol No.: RABGRD4048

Title of Study: Symptoms of gastroesophageal reflux disease (GERD): Classification of adult subjects suffering from typical GERD symptoms and description of the most frequent symptom profiles and characteristics – European observational study

NCT No.: Not applicable

Document No.:

Clinical Registry No.: CR016519

Study Center(s): The observational study was conducted in 5 countries: Russia, Spain, Italy, Greece, and France.

Publication (Reference): Not applicable.

Study Period: First Patient in: 06 JUN 2010; Last Patient out: 30 JUN 2011

Phase of Development: Observational study

Objectives: The primary objective of this observational study was to determine a classification of adult subjects suffering from typical gastroesophageal reflux disease (GERD) symptoms and to describe the most frequent symptom profiles and characteristics of each defined class. This classification was based on the presence or absence of 13 symptoms and was performed by means of a latent class analysis (LCA).

This classification was considered successful if it allowed homogenous subject subgroups to be defined and if significantly less classification errors than expected from a random assignment to latent classes, were observed.

The secondary objectives were:

1. to verify whether there was an association between latent classes of symptom profiles and explanatory weight-related variables, such as body mass index (BMI) classes (normal, overweight, obese), recent weight changes, waist circumference;

2. to determine latent classes based on symptom profiles, associated with other factors such as: age, history (duration) and characteristics (frequency, intensity…) of GERD symptoms, presence of endoscopic lesions, history of GERD (new patient, recurrence, etc.), GERD management (GERD treatment, type of treatment, etc.).

This study could be considered a clinical success when a classification of adult subjects is obtained, which would help the physician in the analysis of subject symptoms.

Methodology: This was an international, multicenter, observational, transversal, one visit, non-product specific study. A total of 7917 adult subjects were enrolled in the study.

Subjects suffering from GERD and presenting at least one of the typical GERD symptoms (i.e., heartburn and/or regurgitation), at least once a week, in the week prior to the first (and only) study visit were candidates for documentation in this study. Importantly, as this was a non-interventional study, neither changes to the current treatment that the subject received, were required, nor was additional treatment provided by the sponsor.

At each institution, investigators could document 3 to a maximum of 100 consecutive subjects presenting with typical GERD symptoms and fulfilling the in- and exclusion criteria. After receiving the written informed consent from the subject (except in France as reported in an amendment), the investigator, or other qualified and trained member of investigational staff started to document the subject data. The subject's care was not altered as a result of his/her involvement in the study.

After subject's eligibility for this study was confirmed, the subject's characteristics, the history of GERD and GERD management, comorbidities (if any), current typical and atypical GERD symptoms, as well as the results of a physical examination were documented in the Case Report Form (CRF). No blood, urine samples, or other biological samples were taken, and no additional investigations were performed.

An interim analysis of the primary and secondary objectives was performed when specialty sites (i.e., sites of gastroenterologists, endoscopists, and internal medicine specialists) had completed their recruitment. By then, 4185 subjects had been considered for this analysis (enrolled in Spain, Italy, Greece, and Russia).

Number of Subjects (planned and analyzed): A total of 7917 adult subjects were documented in the study. The per-protocol population (i.e., all subjects who met all inclusion and exclusion criteria) consisted of 7700 subjects; 38 subjects (0.5%) from the safety population did not meet one or more inclusion and/or exclusion criteria. In France, 179 subjects (2.3%) from 32 sites that refused a monitoring visit, were included in the safety analysis, however, they were excluded from the per protocol analysis. The primary analysis (i.e., all subjects from the per-protocol population with non-missing indicator variables) was performed on 7434 subjects. A total of 266 subjects were excluded from the primary analysis because of one or more missing indicator variables.

Diagnosis and Main Criteria for Inclusion: Subjects, at least 18 years old, suffering from GERD (established diagnosis of GERD or an occurrence of at least one of the typical GERD symptoms, i.e., heartburn and/or regurgitation, at least once a week, in the last three months) and presenting at least one of the typical GERD symptoms, at least once a week, in the week prior to the first (and only) study visit were candidates for documentation in this observational study.

Test and Reference Product, Dose and Mode of Administration, Batch No.: As this was a non-interventional study, neither changes to the current treatment that the subject received, were required, nor was additional treatment provided by the sponsor.

Criteria for Evaluation: As soon as the Informed Consent Form (ICF) was signed, if applicable, and the inclusion and exclusion criteria were fulfilled, the subject's characteristics were recorded. All available data about comorbidities, but also data about concomitant medication, smoking, drinking, and other lifestyle habits, as well as the main purpose of the visit were entered. A physical examination was performed and the weight change in the last 12 and 24 months was recorded (if available).

Atypical GERD symptoms were collected as well as the current atypical (digestive) GERD symptoms, present in the week prior to the first (and only) study visit. Details about these typical GERD symptoms, their daytime and frequency of occurrence, the possible life factors causing GERD, and the overall

evolution of GERD symptoms in the last 12 months were collected. Current atypical (non-digestive) GERD symptoms were also captured in the CRF. "Warning signs", quality of sleep, as well as the subject's GERD history, were recorded.

The GERD management, including data about GERD non-medical and medical treatment and recommendations for future GERD consultations (if any) were documented.

Adverse drug reactions (ADRs) or Severe ADRs (SADRs), reported by the subject or observed by the physician during the documented visit, were reported in compliance with country-specific regulations concerning the spontaneous reporting of ADRs.

Statistical Methods: The statistical analysis was carried out by Janssen-Cilag EMEA. All analyses were performed using Statistical Analysis Software (SAS version 9.1), except for the LCA, which was performed with Mplus (version 6.11).

The classification of subjects was carried out by means of a LCA, a multivariate type of analysis with categorical variables. The purpose was to classify subjects into a set of latent classes, based on indicator variables ("present/absent" type of variables). In this study there were 13 indicators with a total of 8192 possible response patterns (2^{13}). A stepwise approach was used to determine the optimum number of classes. The classes of subjects were described using demographic data, typical GERD symptoms and other GERD-associated data, weight-related characteristics, etc.

RESULTS:

STUDY POPULATION:

Overall, 7917 subjects from five different countries (France, Italy, Spain, Greece, and Russia) participated in this single-visit observational study.

There were 38 deviations to the inclusion and exclusion criteria defined in the protocol and 179 subjects enrolled in France were excluded because the sites refused a monitoring visit. The per-protocol population consisted of 7700 subjects and the primary analysis was performed on 7434 subjects. Most participants (52.0%) were female, the mean age was 52.0 years (SD=14.9). Overall, BMI categories showed that 39.1% of the participating subjects was lean, whereas 37.3% was overweight and 23.6% obese. During the 12 months before the study visit, 27.7% of subjects lost weight, whereas 34.0% had gained weight. Most of the time the weight loss or gain was between 0 to 2 kg. Of all subjects, 26.5% smoked, 38.3% drank alcohol, 57.8% took concomitant medications, and 44.6% tried to adopt a lifestyle habit.

EFFICACY RESULTS:

A history of GERD was known in 74.3% of cases and 66.1% were medically treated for GERD. The most commonly used GERD medical treatment consisted in a PPI treatment (76.3% of subjects who used medical GERD treatment). GERD non-medical treatment consisted in most cases (51.4% of subjects) in a continuation of the subjects' lifestyle habits or the start with new lifestyle habits (38.9%).

Most subjects complained of moderate heartburn and mild regurgitation (53.9% and 37.1%, respectively). Atypical GERD digestive symptoms were reported by 79.9% of the subjects, of which epigastralgia (overall 42.7%) and eructation (overall 42.5%) occurred most.

The LCA was performed on 7434 subjects, on 12 indicator categorical variables. One indicator variable *digestive bleeding, anemia* was excluded because probability was very low in all classes in all investigated models. The LCA yielded 5 latent classes. Class 1 (1598 subjects) represented a very high probability ($\leq$0.8 to $\leq$1.0) of daytime heartburn and regurgitation and a high probability ($\leq$0.6 to <0.8) of

nighttime heartburn and/or regurgitation. The probability of all other symptoms was higher than in any of the other classes. Class 2 (845 subjects) was characterized by the absence of heartburn and regurgitation during the day but presence during the night. Nighttime problems were also reflected by a medium probability (≤0.3 to <0.6) of nocturnal awakenings and nightmares. Class 3 (2375 subjects) showed a high probability (≤0.6 to ≤0.8) of daytime as well as nighttime heartburn and/or regurgitation. A medium probability (≤0.3 to <0.6) was seen in the atypical symptoms (S4-S6) and sleep disorders. Class 4 (1181 subjects) also had a very high probability (≤0.8 to ≤1.0) of daytime heartburn and regurgitation, however, the probability of nighttime heartburn and/or regurgitation was low (<0.3). The probability of the rest of the symptoms was comparable to Class 3, except for nocturnal awakening and nightmares. The low probability (<0.3) of nocturnal awakening and nightmares corresponded with the absence of the nighttime core symptoms. Class 5 (1435 subjects) differed from the other classes because there was only one symptom with a high probability (≤0.6 to ≤0.8): daytime heartburn. Daytime regurgitation had a medium probability (≤0.3 to ≤0.6), whereas the probability of all other symptoms was low (<0.3).

The relation between the classification in 5 latent classes and subject- and GERD-related factors was explored using multinomial logistic regression modeling.

In this multivariate model, factors with a significant effect on the latent classes were: country, age, gender (male), smoking, alcohol use, low-fat diet, waist circumference, recent weight gain (more than 5kg), elevated triglycerides, metabolic syndrome, and medical GERD treatment.

PHARMACOKINETIC AND PHARMACODYNAMIC RESULTS:

Not applicable.

SAFETY RESULTS:

The safety analysis set consisted of all included subjects. The subjects from the sites that refused monitoring were included in this analysis.

The incidence of ADRs was low: 10 subjects (0.1%) experienced 14 ADRs, which were reported as mild or moderate. The ADRs were considered doubtfully, possibly, probably, or very likely related to the suspected drug and 3 lead to a permanent discontinuation of the suspected drug.

No SADRs were reported and no deaths occurred during the study.

STUDY LIMITATIONS:

No notable study limitations were identified by the Sponsor.

CONCLUSION(S):

The results of this study made it possible to determine a classification of adult subjects suffering from typical GERD symptoms and to describe the most frequent symptom profiles and characteristics.

A detailed classification of GERD symptoms will certainly help determining a specific patient profile. The understanding of the link between the various types of GERD symptoms is important for screening and applying preventive measures for GERD and its potential complications.