Clinical Study Synopsis

Name of Company: **AstraZeneca K.K.**	**Volume:**	(For national authority use only)
Name of Finished Product: **Nexium**	**Page:**	
Name of Active Ingredient: **Esomeprazole magnesium**		

Title of Study: An 8-week, open label, multicentre study to assess the efficacy of esomeprazole 20 mg once daily in subjects with continuing symptoms of heartburn following treatment with a previous rabeprazole

Protocol Number: D961HL00002

Study Period: **Phase of Development:** IV

Date of first enrolment: 25 August 2011

Date of last completed: 31 January 2012

Investigators: 19 principal investigators from four countries participated.

Study Centres: The study was conducted at 19 active sites in China, Malaysia, Philippines and Singapore.

Publications: None.

Objectives:

The **primary objective** of this study was to assess the efficacy of esomeprazole 20 mg once daily in subjects who still had heartburn after receiving rabeprazole 10 mg once daily for at least 4 weeks by evaluating the change in the frequency of heartburn during the 7-day period prior to the 8 week visit (Visit 3) compared to the frequency of heartburn during the 7-day period prior to Visit 1, after treatment with esomeprazole 20 mg.

The **secondary objectives** were:

• To assess the efficacy of esomeprazole 20 mg by evaluating the change in the frequency of heartburn during the 7-day period prior to the 4 week visit (Visit 2) compared to the frequency of heartburn during the 7-day period prior to Visit 1;

• To assess the efficacy of esomeprazole 20 mg by evaluating the changes in the maximum severity of heartburn during the 7-day period prior to the 4 week visit (Visit 2) and the 8 week visit (Visit 3) compared to the maximum severity of heartburn during the 7-day period prior to Visit 1;

• To assess the efficacy of esomeprazole 20 mg by evaluating the changes in the maximum severity and frequency of epigastric pain and acid regurgitation during the 7-day period prior to the 4 week visit (Visit 2) and the 8 week visit (Visit 3) compared to those during the 7-day period prior to Visit 1;

• To assess the efficacy of esomeprazole 20 mg by evaluating the severity and frequency of the subject-reported gastroesophageal reflux disease (GERD) symptoms:

o Rate and time to sustained resolution of each symptom after 4 and 8 weeks of treatment;

o Rate and time to complete resolution of each symptom after treatment of esomeprazole 20 mg;

• To assess the efficacy of esomeprazole 20 mg by evaluating the subject satisfaction after treatment of esomeprazole.

The **safety objective** of this study was to assess the safety and tolerability of esomeprazole 20 mg by evaluating of adverse events (AEs) and vital signs (blood pressure and pulse rate).

Study Design: This was a phase IV, open-label and multicentre study. The study consisted of a screening visit, which was also the baseline visit, and an 8-week treatment period with two assessment visits (at Week 4 and Week 8). Study treatment was started at Visit 1 in subjects who were eligible for the study.

Number of Subjects (planned and analysed): The study planned to enrol 100 subjects to allow 85 subjects to complete the treatment period. The actual numbers of subjects who were screened and completed the treatment period were 108 and 100 subjects, respectively. Of the 108 subjects screened, 107 subjects were enrolled and included in the safety set, 104 were included in the full analysis set (FAS) and 100 were included in the per-protocol set (PPS).

Diagnosis and Main Criteria for Inclusion: The subjects with reflux esophagitis who had uncontrolled symptoms of heartburn despite having taken rabeprazole 10 mg daily for at least 4 weeks prior to study entry. Main inclusion criteria were:

• Informed consent.
• Male or female aged 20 years or more.
• The subject had to be currently taking rabeprazole for at least the last 4 weeks and for at least 4 days a week in the past 7 days prior to Visit 1.
• Had persisting symptoms of heartburn for at least 2 days during the past 7 days prior to Visit 1.

Test Product, Dose and Mode of Administration, and Batch Numbers: Oral administration of esomeprazole 20 mg daily, taken once daily (with water, 30 minutes before breakfast) for 8 weeks.
Batch numbers: 1108037, 1103098, 1108063, NA19022, MM18982, 60001142.

Reference Therapy, Dose and Mode of Administration, and Lot Numbers: Not applicable.

Duration of Treatment: 8 weeks.

Criteria for Evaluation:

Efficacy:

The primary efficacy endpoint was the change in investigator-reported frequency of heartburn during the 7-day period prior to 8 week visit (Visit 3) compared to the frequency of heartburn during the 7-day period prior to Visit 1.

The secondary endpoints were:

• The change in the frequency of heartburn during the 7-day period prior to the 4 week visit (Visit 2) compared to the frequency of heartburn during the 7-day period prior to Visit 1.
• The changes in the maximum severity of heartburn during the 7-day period prior to the 4 week visit (Visit 2) and the 8 week visit (Visit 3) compared to the maximum severity of heartburn during the 7-day period prior to Visit 1.
• The changes in the maximum severity and frequency of epigastric pain and acid regurgitation during the 7-day period prior to the 4 week visit (Visit 2) and the 8 week visit (Visit 3) compared to those during the 7-day period prior to Visit 1.
• Subject-reported symptom resolution (sustained resolution for at least 7 days and complete resolution).
• Subject satisfaction.

Safety:

Safety endpoints were the number of subjects with AEs reported, change from baseline to week 4 and to week 8 in vital signs (blood pressure and pulse rates) and physical examinations.

Statistical Methods:

Efficacy:

Both the FAS and the PPS were used for the analysis of the primary variable but only FAS was used in the analysis of secondary efficacy variables. The FAS was the primary efficacy analysis set.

The change in the frequency and maximum severity of the GERD symptoms of heartburn, acid regurgitation and epigastric pain from during the 7-day period prior to Visit 1 to the 7-day period prior to week 4 visit (Visit 2) or week 8 visit (Visit 3) were analysed by the Wilcoxon signed rank test at two-sided 5% level.

Sustained resolution and complete resolution of each subject-reported symptom were both handled as an event. The time to event from the starting day of investigational product administration was analysed by Kaplan-Meier (K-M) method and K-M plots of sustained resolution and complete resolution were summarised.

Subject satisfaction at Visit 3 was summarised using descriptive statistics.

Safety:

The safety population was used for the safety analysis. Safety variables were analysed using descriptive statistics.

Efficacy Results:

Primary endpoint: The mean (standard deviation [SD]) change of investigator-reported frequency of heartburn from Visit 1 to Visit 3 from both the last observation carried forward (LOCF) and observed data was -3.0 (2.4) on a 0-7 scale in the FAS. Similar results were observed in the PPS (-3.1 [2.3] on a 0-7 scale). The decrease in heartburn frequency after 8-week treatment of esomeprazole was statistically significant in both the FAS and PPS ($p<0.001$ for both populations based on Wilcoxon signed rank test).

The results of the secondary endpoints supported the results of the primary endpoint.

In the FAS (LOCF data), the mean (SD) changes of investigator-reported frequency of heartburn, epigastric

pain and acid regurgitation from Visit 1 to Visit 2 were: -2.3 (2.8), -0.7 (2.9) and -2.2 (3.1), respectively, on a 0-7 scale. The mean (SD) changes of frequency of epigastric pain and acid regurgitation from Visit 1 to Visit 3 were: -1.3 (2.8) and -2.9 (3.0), respectively, on a 0-7 scale. There was a decrease in frequency after 4 weeks of esomeprazole treatment and a further decrease after 8 weeks of treatment in all GERD symptoms, and all changes were statistically significant.

In terms of maximum severity of GERD symptoms, a decreasing proportion of subjects reported severe or moderate symptoms from Visit 1 to Visit 2 and from Visit 2 to Visit 3 for heartburn, epigastric pain and acid regurgitation. All the changes were statistically significant. Shift tables confirmed that the majority of subjects had a decrease in symptom severity during the study.

In the subgroup analyses by country, age, gender and weight, the data showed a consistent mean decrease in frequency of heartburn, epigastric pain and acid regurgitation frequencies in each subgroup. Data for the country subgroups of Singapore and Malaysia could be interpreted due to the small number of subjects.

Based on subject-reported symptoms, the proportion of subjects who achieved sustained resolution and complete resolution increased over time for heartburn, epigastric pain and acid regurgitation. The median time for sustained resolution of heartburn, epigastric pain and acid regurgitation was: 21.0 days (95% confidence interval [CI]: 14.0-28.0), 12.5 days (95% CI: 7.0-20.0) and 11.0 days (95% CI: 6.0-21.0), respectively. The median time for complete resolution of epigastric pain and acid regurgitation was:

55.0 days (95% CI: 45.0-not applicable) and 49.5 days (95% CI: 44.0-not applicable), respectively. Less than 50% (49%) of subjects achieved complete resolution of heartburn at the end of the study.

From the results of the Patient Satisfaction Questionnaire, over 90% of the subjects reported positive responses (got slightly better or better; and partially satisfied or fully satisfied).

Safety Results:

Of the 107 subjects in the safety population, 11 (10.3%) subjects had at least one AE, and the most commonly reported AE by preferred term (PT) was diarrhoea (2 [1.9%] subjects). Three (2.8%) subjects experienced at least one study drug-related AE (PTs: abdominal pain, diarrhoea, nausea, vomiting and dysgeusia). One (0.9%) subject reported a severe AE (dysgeusia) which was considered study drug-related.

No deaths were reported in this study. Two (1.9%) subjects experienced serious adverse events (SAEs) (events: inguinal hernia and typhoid fever) and the two SAEs were considered not related to study drug.

Both SAEs resolved. Two (1.9%) subjects discontinued from the study due to AEs (dysgeusia and non-cardiac chest pain). No other significant AEs were reported.

At the end of the study, 2 (1.9%) subjects had ongoing AEs which were all related to study drug. The ongoing AEs were diarrhoea, abdominal pain, nausea and vomiting (one event each).

No clinically relevant changes in vital signs and physical examinations were observed during 8 weeks of study drug treatment.

Date of Report: 27 April 2012