AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: esomeprazole 40 mg
ACTIVE INGREDIENT: esomeprazole magnesium

Study No: D961HL00001
An 8-week, open label, multicentre study to assess the efficacy of esomeprazole 40 mg once daily in subjects with continuing symptoms of heartburn following treatment with a previous rabeprazole

Developmental Phase: IV
Study Completion Date: July 2011
Date of Report: 30 September 2011

OBJECTIVES:

The primary objective was to assess the efficacy of esomeprazole 40 mg once daily in subjects who still had heartburn after receiving rabeprazole 20 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 40 mg.

The secondary objectives were:

- To assess the efficacy of esomeprazole 40 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 40 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 40 mg by evaluating the changes in the maximum severity and severity 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 the maximum severity of heartburn during the 7-day period prior to Visit 1.
- To assess the efficacy of esomeprazole 40 mg by evaluating the severity and frequency of subject-reported gastro-oesophageal reflux disease (GERD) symptoms:
  - Sustained resolution of each symptom after 4 and 8 weeks of treatment
  - Time to complete resolution after treatment of esomeprazole 40 mg.
- To assess the efficacy of esomeprazole 40 mg by evaluating subject satisfaction after treatment with esomeprazole.
- The safety objective was to assess the safety and tolerability of esomeprazole 40 mg by evaluating adverse events (AEs) and vital signs (blood pressure and pulse rate).

METHODS:

Subjects, with a history of reflux oesophagitis and with continuing heartburn after previous treatment with rabeprazole, were expected to be identified at a routine visit to their physician. These subjects, if eligible, were enrolled in the study and administered esomeprazole 40 mg orally, once daily, for 8 weeks. At Week 4 (Visit 2) subjects returned to the clinic for a review of their GERD symptoms and for safety assessments and at Week 8 (Visit 3), at the end of treatment, subjects returned for final assessments.

Diagnosis and main criteria for inclusion:
Subjects aged 20 years or older with a history of reflux oesophagitis, verified by endoscopic examination in the past, who were receiving rabeprazole 20 mg once daily for at least 4 weeks before the study and who were still experiencing symptoms of heartburn in the 7 days leading up to Visit 1. Subjects were not to have used other proton pump inhibitors and/or histamine-2 receptor antagonists during their treatment with rabeprazole nor have been treated with esomeprazole during the 12 weeks before enrolment.

Test product, dose and mode of administration, batch numbers:
Esomeprazole 40 mg (one tablet) taken daily before breakfast.

Duration of treatment:
8 weeks.

Reference therapy, dose and mode of administration, batch number:
None

Statistical methods:
The Full Analysis Set (FAS) comprised those subjects with at least one assessment of efficacy after the initiation of study treatment and who did not deviate from any major inclusion criteria.
The Per-protocol Set (PPS) comprised those subjects in the FAS who had no major protocol violations or deviations that may affect the efficacy assessment and had good compliance (defined as compliance greater than or equal to 75% and less than or equal to 125%).
The Safety Analysis Set comprised those subjects who had at least one dose of study medication and for whom any post-dose data were available.

Primary efficacy
The change in frequency of heartburn during the 7-day period prior to Visit 1 (screening) to the 7-day period prior to Visit 3 (Week 8) was summarised and analysed using the Wilcoxon signed-rank test in the FAS and PPS. If the data were missing at Visit 3 (Week 8) or the subject had discontinued prematurely, then the last available observation after baseline was carried forward and used in the analysis. As a sensitivity analysis, the primary variable was also summarised and analysed as above using observed data.

Secondary efficacy
Investigator-reported GERD symptoms: The change in frequency of heartburn during the 7-day period prior to Visit 1 (screening) to the 7-day period prior to Visit 2 (Week 4) and the change in frequency of epigastric pain and acid regurgitation during the 7-day

period prior to Visit 1 (screening) to the 7-day period prior to Visit 2 (Week 4) and the 7-day period prior to Visit 3 (Week 8), were analysed as per the primary endpoint for the FAS. The change in maximum severity of heartburn, epigastric pain and acid regurgitation during the 7-day period prior to Visit 1 (screening) to the 7-day period prior to Visit 2 (Week 4) and the 7-day period prior to Visit 3 (Week 8) were summarised categorically and analysed using the Wilcoxon signed-rank test for the FAS.

Subject-reported GERD symptoms: The time to sustained resolution of heartburn, acid regurgitation and epigastric pain was analysed using the Kaplan-Meier method for the FAS. Subjects who did not achieve sustained resolution were censored at the time of completion or withdrawal. The time to complete resolution of heartburn, acid regurgitation and epigastric pain was analysed using the Kaplan-Meier method for the FAS. Subjects who did not achieve complete resolution were censored at the time of completion or withdrawal (subjects who withdrew were censored regardless of whether they were symptom free at the time of withdrawal). The number of subjects without heartburn, epigastric pain and acid regurgitation during the 7-day period prior to Week1, Week 2, Week 4 and Week 8 were summarised for the FAS.

Subject Satisfaction: The results for each of the three questions in the subject satisfaction questionnaire collected at Visit 3 (Week 8) were summarised for the FAS.

Safety: Safety variables were summarised using descriptive statistics.

RESULTS:

Disposition and baseline data: Safety Analysis Set, 100 subjects; FAS, 96 subjects; PPS, 91 subjects.
A total of 94 subjects completed the 8-week treatment period. Of the seven subjects who prematurely withdrew from the study, most chose to withdraw for personal reasons. All subjects were at least 75% compliant in taking study medication. The mean age was 51.2 years; 59.4% subjects were male and 40.6% were female. In the 7 days before Visit 1 (i.e., baseline), the mean frequency of heartburn, epigastric pain and acid regurgitation was 4.6, 2.8 and 3.4 days, respectively.

Primary efficacy (FAS and PPS): a mean decrease of 3.3 days (standard deviation [SD] 2.36) in the frequency of heartburn in the 7-day period before Week 8 compared with baseline; the change was statistically significant (p-value <0.001). Results for the PPS were similar (-3.2; SD 2.38 days; p-value <0.001).

Secondary efficacy (FAS):

- Mean decrease of 2.6 days (SD 2.82) in the frequency of heartburn in the 7-day period before Week 4 compared with baseline; the change was statistically significant.
- Mean decreases of 1.7 days (SD 2.77) and 2.4 days (SD 2.19) in the frequency of epigastric pain and acid regurgitation, respectively, in the 7-day period before Week 8. The mean change from baseline at Week 4 was similar. All changes were statistically significant.
- A decrease in the maximum severity of heartburn, epigastric pain and acid regurgitation in the 7-day periods before Week 4 and Week 8. The change from

baseline for all symptoms and at both time points was statistically significant.

- Median time to sustained resolution of heartburn, epigastric pain and acid regurgitation was 19 days (95% confidence interval [CI]: 11.0, 32.0), 13 days (95% CI: 4.0, 22.0) and 9 days (95% CI: 6.0, 18.0), respectively. The Kaplan-Meier estimate of the rate of sustained resolution of heartburn, epigastric pain and acid regurgitation at Week 8 was 74.9% (95% CI: 65.7, 83.2), 83.9% (95% CI: 75.6, 90.6) and 79.2% (95% CI: 70.4, 86.8), respectively.
- Median time to complete resolution of heartburn, epigastric pain and acid regurgitation was 50 days (95% CI: 38.0, -), 45 days (95% CI: 31.0, 50.0) and 45 days (95% CI: 29.0, -), respectively. The Kaplan-Meier analysis estimate of the rate of complete resolution of heartburn, epigastric pain and acid regurgitation at Week 8 was 51.7% (95% CI: 41.9, 62.4), 62.8% (95% CI: 52.9, 72.6) and 56.0% (95% CI: 46.1, 66.4), respectively.
- In the subject satisfaction questionnaire at 8 weeks 95.7% of subjects felt their quality of life had either got better or slightly better. Most subjects (91.4%) were either fully satisfied or partially satisfied with their current medication. The majority of subjects (87.1%) preferred the current rather than the previous medication.

Safety:

- Twelve (12.0%) subjects had 25 AEs.
- Two (2.0%) subjects reported an AE of nasopharyngitis and the remaining AEs were reported by single subjects only. Two (2.0%) subjects had AEs that were considered to be related to study medication (dry mouth, dizziness, constipation and chest discomfort).
- All AEs were mild in intensity except for one of urticaria that was of moderate intensity.
- There were no deaths or SAEs reported during the study.
- Two subjects discontinued study medication due to AEs of constipation, and epistaxis and nasopharyngeal pain.
- No changes of note were observed in blood pressure or pulse.

Conclusions

Treatment with esomeprazole 40 mg was effective and well tolerated in subjects with GERD symptoms that were not well controlled by rabeprazole 20 mg. In addition, after 8 weeks of esomeprazole, most subjects in the study stated that their quality of life had improved.