AstraZeneca

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Esomeprazole 40 mg (as esomeprazole magnesium trihydrate 44.5mg) as oral MUPS tablets; esomeprazole 20 mg (as esomeprazole magnesium trihydrate 22.3mg) as oral MUPS tablets
ACTIVE INGREDIENT: Esomeprazole 40 mg (as esomeprazole magnesium trihydrate 44.5mg) as oral MUPS tablets; esomeprazole 20 mg (as esomeprazole magnesium trihydrate 22.3mg) as oral MUPS tablets

Study No: D9612L00078
An open-label, parallel-group, multi-centre study to determine the effect of treatment with esomeprazole for six months on histological markers of esophageal epithelial acid-related disease in patients with upper GI symptoms: the HEARD study (Histology of the Esophagus in Acid-Related Disease)

Developmental phase: IIIb

Study Completion Date: Last Subject Last Visit 07 Jun 2007; Database Lock/Clean File 20 Aug 2008

Date of Report: TBD

OBJECTIVES:

Primary objective

To evaluate the changes from baseline in measures of esophageal epithelial acid-related disease (squamous cell proliferation (Ki-67 expression) and traditional histology) from baseline following six months treatment with acid suppressive therapy with esomeprazole in patients with upper GI symptoms.

Secondary objectives

1. To identify and examine the changes from baseline in immunohistochemical markers of esophageal epithelial acid-related disease after six months treatment with acid suppressive therapy with esomeprazole in patients with upper GI symptoms.

2. To examine differences in immunohistochemical and traditional histological markers of esophageal epithelial acid-related disease at baseline between three patient groups: (A) esophagitis, (B) no esophagitis but dominant symptoms of

heartburn or acid regurgitation, and (C) no esophagitis but presence of upper GI symptoms that include at least one of epigastric pain, epigastric discomfort, non-dominant heartburn or non-dominant acid regurgitation.

3. To examine the potential of various factors (demographic, endoscopic and symptomatic) to predict the presence and intensity of immunohistological and traditional histological markers of esophageal epithelial acid-related disease at baseline and in response to six months of acid-suppressive therapy with esomeprazole.

4. To evaluate the safety and tolerability of esomeprazole through examination of adverse, serious adverse events and laboratory data.

METHODS:

This is a randomised, open-label, parallel-group, multi-centre study that will evaluate changes in esophageal histological and immunohistochemical markers of cellular injury, inflammation and repair in patients with upper GI symptoms treated with esomeprazole for a period of six months. All patients with erosive esophagitis will receive continuous esomeprazole 40 mg once daily for six months. Those without erosive esophagitis will be divided between two groups dependent on the presence of dominant reflux symptoms or not, and will be randomised to receive either continuous esomeprazole 40 mg (once daily) or discontinuous esomeprazole 20 mg (once daily as needed).

Target subject population

Adult subjects presenting with a minimum three-month history of upper GI symptoms (including any of the following symptoms: epigastric pain, epigastric discomfort, heartburn, acid regurgitation; with or without excessive burping/belching, increased abdominal bloating, nausea, feeling of abnormal or slow digestion, or early satiety) with symptoms on at least two days in the past week prior to Visit 1 and at least moderate severity (on a none, mild, moderate, severe scale) on at least one of those days.

Investigational product, dosage and mode of administration

Either esomeprazole 40 mg (as esomeprazole magnesium trihydrate 44.5 mg) or 20 mg (as esomeprazole magnesium trihydrate 22.3 mg) in oral MUPS tablet form.

Comparator, dosage and mode of administration

All those in patient group A (erosive esophagitis (EE)) will receive esomeprazole 40 mg once daily. Patients in group B (no EE, reflux symptom dominant) and C (no EE, non-reflux symptom dominant) will be randomised in a 1:1 ratio to either continuous (esomeprazole 40 mg once daily) or discontinuous (esomeprazole 20 mg as needed but no more than once daily) treatment.

Duration of treatment

Six months

Outcome variables

Efficacy

Primary outcome variable:

- The primary variable will be the change from baseline after 6 months in the level of Ki-67 expression and histological markers (basal cell layer thickness, papillary length, dilated intercellular spaces) of esophageal epithelial acid-related disease after acid-suppressive therapy with esomeprazole in patients with upper GI symptoms.

Secondary outcome variables:

- The presence and changes in immunohistochemical markers of esophageal epithelial acid-related disease after six months treatment with different levels of acid suppression with esomeprazole in patients with upper GI symptoms.
- The difference in the histological and immunohistochemical markers of esophageal epithelial acid-related disease at baseline between the three patient groups: (A) esophagitis, (B) no esophagitis but dominant symptoms of heartburn or acid regurgitation, and (C) no esophagitis but presence of upper GI symptoms that include at least one of epigastric pain, epigastric discomfort, non-dominant heartburn or non-dominant acid regurgitation.
- The utility of various factors (demographic, endoscopic and symptomatic) for predicting the presence and intensity of immunohistological and traditional histological markers of esophageal epithelial acid-related disease at baseline and in response to six months acid-suppressive therapy with esomeprazole.

Patient reported outcomes (PROs):
Scores, and change in scores from baseline, of the Global Overall Symptom (GOS) severity scale, the Quality of Life in Reflux and Dyspepsia (QoLRAD) questionnaire, Gastrointestinal Symptoms Rating Scale (GSRS) questionnaire and Reflux Disease Questionnaire (RDQ) will be examined as possible symptomatic predictors of levels and changes in immunohistological and traditional histological markers of esophageal epithelial acid-related disease after six months of acid-suppressive therapy with esomeprazole.

Health economics: Not applicable

Pharmacokinetic: Not applicable

Pharmacodynamic: Not applicable

Safety:
The incidence, severity and duration of adverse events for the two treatment groups.
The number and proportion of patients with normal and abnormal physical findings at baseline and at the end of the treatment period, as well as the number of patients whose normal findings at baseline changed to abnormal.
Individual and mean changes from baseline of laboratory assessments for the two treatment groups.

Genetics: Not applicable

Statistical methods

All enrolled patients with a minimum amount of data will be included in the analysis. Due to the exploratory nature of this study, all variables will be presented using descriptive statistics and statistical modelling.

The change from baseline in the level of Ki-67 expression and histological markers of esophageal epithelial acid-related disease within each treatment group will be summarized descriptively.

The change in immunohistochemical markers of esophageal epithelial acid-related disease after six months treatment will be presented descriptively for erosive esophagitis patients. Analysis of covariance (ANCOVA) will be used to estimate the treatment difference in the change from baseline of the histological and immunohistochemical markers of esophageal epithelial acid-related disease after 6 months in patients with non-erosive esophagitis. Treatment difference will be estimated with the adjustment of patient group and centre effect if applicable. The baseline value will be considered as a covariate.

Differences in histological and immunohistochemical markers of esophageal epithelial acid-related disease at baseline between three patient groups (A, B and C) will be estimated using an analysis of variance (ANOVA).

Stepwise regression technique will be used to identify significant factors associated with levels and changes in immunohistological and traditional histological markers of esophageal epithelial acid-related disease at baseline and in response to a 6-month course of acid-suppressive therapy.

Adverse events, laboratory data, vital signs and physical findings will be presented descriptively.

RESULTS:

Symptoms and Patient Reported Outcomes

Daily Symptoms – Diary: Per mean daily score (3 month period), subjects in Group A demonstrated the greatest decrease in symptoms from month 0-3 to month 3-6.

Medical Intake: Group A subjects had the highest medication intake (overall 99.3% of days), followed by the other esomeprazole 40 mg groups (Group C E40 96.6%; Group B E40 96.5%). The esomeprazole 20 mg groups had overall lower medication intake (Group B E20 70.9%; Group C E20 65.4%).

Antacid Intake: Group C E20 had the highest antacid (rescue medication) intake (overall mean 1.1 tablets per day), following by Group B E20 and Group C E40 (both 0.8), Group B E40 (0.6) and finally Group A (0.4).

GOS: All patient groups demonstrated an improvement (decreased GOS score) from visit 1 to visit 2, and all groups demonstrated relatively little change from visit 2 to visit 3. Group A demonstrated the greatest change in GOS score: -2.9 points (7-point scale) from visit 1 to visit 2 and from visit 1 to visit 3 (i.e. no change from visit 2 to visit 3). In contrast, Group C E20 demonstrated the least change in GOS score: -1.5 points from visit 1 to visit 2 and from visit 1 to visit 3 (i.e. no change from visit 2 to visit 3). Group B E40 demonstrated -2.5 point change in GOS score from visit 1 to visit 2 and -2.2 point change from visit 1 to visit 3. Group B E20 demonstrated -1.8 point change in GOS score from visit 1 to visit 2 and -1.9 point change from visit 1 to visit 3. Group C E40 demonstrated -2.0 point change in GOS score from visit 1 to visit 2 and -2.1 point change from visit 1 to visit 3. For visit 1 to visit 3: the overall change in GOS score for all patient groups was statistically significant ($p<0.0001$); the overall group difference in GOS score for E40 patients from was statistically significant ($p=0.02$); for E40 patients, Group A vs. Group B was statistically significant ($p=0.036$), and both Group A vs. Group C and Group A vs. Groups B + C were both statistically significant ($p=0.007$); in contract, for E40 patients, Group B vs. Group C was not statistically significant ($p=0.472$), and for E20 patients, Group B vs. C was not statistically significant ($p=0.191$). According to GOS: 69.2% of Group A patients, or 52 patients, had symptom relief at visit 3; in contrast, 40.3% of Group C E20 patients, or 77 patients, had symptom relief at visit 3; finally, 55.7% of Group B E40 patients, 50.0% of Group C E40 patients and 48.7% of Group B E20 patients had symptom relief at visit 3. Examining Groups B + C, 52.9% of E40 patients, or 157 patients, and 44.4% of E20 patients, or 153 patients, had symptom relief at visit 3.

QoLRAD: From visit 1 to visit 3, improvement (increase in QoLRAD score) was observed for all patient groups within all domains (i.e. Emotional Distress, Sleep Disturbance, Food/Drink Problem, Physical/Social Functioning, Vitality), and all improvements were statistically significant ($p<0.0001$ for all, except for the Group C E20 patients within the Sleep Disturbance and Physical/Social Functioning domains where $p=0.0002$). Examining group differences: for E40 patients, except for the Food/Drink Problem domain, there was no significant difference between Group A and Group B or between Group B and Group C, and for all domains improvement was greater in Group A vs. Group C (or Groups B + C); for E20 patients, for 3 domains (Emotional Distress, Sleep Disturbance, Physical/Social Functioning), improvements were greater in Group B than in Group C; for Group B, there was no significant difference between E40 and E20 patients for all domains, except Food/Drink Problem; for Group C, there was no significant difference between E40 and E20 patients for all domains, except Vitality; for Group B + C, there was no significant difference between E40 and E20 patients for all domains, except Food/Drink Problem and Vitality.

RDQ: From visit 1 to visit 3, overall improvement (decrease in RDQ score) was observed for all patients within all domains (i.e. Heartburn, Epigastric Pain, Regurgitation, GERD), and all improvements were statistically significant ($p<0.0001$ for all, except for the Group C E20 patients within the Heartburn domain where $p=0.0042$ and within the Regurgitation domain where $p=0.0004$). According to RDQ, for the Epigastric Pain domain: 55.8% of Group A patients were asymptomatic at visit 3; in contrast, 11.7% of Group C E20 patients were asymptomatic at visit 3; finally, 32.9% of Group B E40 patients, 28.2% of Group C E40 patients and 18.4% of Group B E20 patients were asymptomatic at visit 3. For the GERD domain: 50.0% of Group A patients

were asymptomatic at visit 3; in contrast, 14.5% of Group B E20 patients were asymptomatic at visit 3; finally, 24.4% of Group C E40 patients, 21.5% of Group B E40 patients and 15.6% of Group C E20 patients were asymptomatic at visit 3. Examining group differences in terms of proportion of patients asymptomatic at visit 3: for the Epigastric Pain domain, E40 patients scored better than E20 patients for Group B ($p=0.028$), Group C ($p=0.014$) and Groups B + C ($p=0.001$); for the GERD domain, E40 patients scored better than E20 patients for Groups B + C ($p=0.072$) but there was no difference for Group B ($p=0.185$) or Group C ($p=0.174$).

GSRS: From visit 1 to visit 3, improvement (decrease in GSRS score) was observed for all patient groups within all domains (i.e. Reflux, Abdominal Pain, Indigestion, Diarrhoea, Constipation, Overall GSRS), and all improvements were statistically significant, except for the Diarrhoea domain (Group A, Group B E20, Group C E40 and Group C E20 patients) and the Constipation domain (Group B E40, Group C E40 and Group C E20) where $p>0.05$. Examining overall GSRS score changes from visit 1 to visit 3: for E40 patients, the overall group difference was statistically significant ($p=0.01$ for RAI domains), as was Group A vs. Group B ($p=0.019$ for RAI domains), Group A vs. Group C ($p=0.006$ for RAI domains) and Group A vs. Groups B + C ($p=0.004$ for RAI domains), whereas Group B vs. Group C was not significant ($p=0.609$ for all domains); similarly, for E20 patients, Group B vs. Group C was not significant ($p=0.12$ for all domains). In terms of group differences: for Group B, for all domains, there was no significant difference between E40 and E20 patients; for Group C and Groups B + C, for all domains except Reflux (within which E40 patients scored better than E20 patients), there was no significant difference between E40 and E20 patients.

Safety Data

Exposure: Mean exposure was 154 days and 37.7 mg/day for E40 patients vs. 147 days and 13.0 mg/day for E20 patients.

Discontinuation: Nine E40 patients (4.3%) were discontinued due to AEs vs. 2 E20 patients (1.3%); 31 E40 patients (14.8%) were discontinued due to other reasons vs. 29 E20 patients (19.0%); 169 E40 patients (80.9%) were not discontinued vs. 122 E20 patients (79.7%).

Adverse Events: For E40, 90 patients (43.1%) had any AE and 2 patients (1.0%) had an SAE; for E20, 60 patients (39.2%) had any AE and 1 patient (0.7%) had an SAE. E40 patients experienced 187 AEs and E20 patients experienced 121 AEs. No deaths were reported in this study. The most prevalent system organ class associated with AEs for the study was GI disorders (40 E40 patients (19.1%) vs. 15 E20 patients (9.8%)), followed by: infections/infestations (28 E40 patients (13.4%) vs. 21 E20 patients (13.7%)); CNS disorders (13 E40 patients (6.2%) vs. 13 E20 patients (8.5%)); MSK/CT disorders (14 E40 patients (6.7%) vs. 6 E20 patients (3.9%)); injury, poisoning, etc (10 E40 patients (4.8%) vs. 6 E20 patients (3.9%)); and general disorders (5 E40 patients (2.4%) vs. 6 E20 patients (3.9%)). The most prevalent reported event associated with AEs for the study was nasopharyngitis (7 E40 patients (3.3%) vs. 8 E20 patients (5.2%)), followed by: diarrhoea (9 E40 patients (4.3%) vs. 5 E20 patients (3.3%)); nausea (7 E40 patients (3.3%) vs. 4 E20 patients (2.6%)); sinusitis (6 E40 patients (2.9%) vs. 4 E20 patients (2.6%)); and headache (5 E40 patients (2.4%) vs. 5 E20 patients (3.3%)).

Histology

Pilot Study and Selection of Antibodies for the Study: Semi-quantitative analysis (immunohistochemistry) and quantitative analysis (image analysis) was performed on esophageal biopsies. Based on evaluation of a pilot sample of 50 subjects (the first 10 subjects from each of the 5 treatment groups with complete pre- and post-treatment biopsies), it was determined that all study samples would be evaluated using the following panel of antibodies (in addition to Mib-1): beta-catenin; MHC2.

Mib-1: Irrespective of the method used, all patient groups at almost all sites (except: Group C E20 at 2 cm above the GEJ via Mib-1 (semi-quantitative); Group B E20, Group C E40 and Group C E20 at 8 cm above the GEJ via Mib-1 (semi-quantitative); Group B E40 at 2 cm and 8 cm above the GEJ via Mib-1 positive area (quantitative)) showed a reduction in proliferative indices post therapy from pre- to post-treatment. Group B E20 patients overall demonstrated the highest proliferative index at the Z-line, and the Z-line biopsies showed the greatest changes.

Beta-catenin: Irrespective of the method used, all patient groups at almost all sites (except: Group A at 2 cm and 8cm above the GEJ via beta-catenin small bubbles (DIS); Group A at 2 cm and 8cm above the GEJ via beta-catenin large bubbles (DIS); Group C E20 at 8cm above the GEJ via beta-catenin large bubbles (DIS)) showed a reduction in DIS indices from pre- to post-treatment. There was no significant differences in the data obtained using small or large bubbles (as defined using the size of an epithelial cell nucleolus, approximately 2 microns). Also, changes in Group C were similar to those in Group B, therefore these groups of patients appear to respond similarly to treatment with esomeprazole from a morphological perspective.

MHC2: The original scoring system used for MHC2 appears to have been too insensitive, therefore no significant results are available for MHC2 from data obtained using this system.