AstraZeneca

DC-QBE-0019

STUDY REPORT SUMMARY

ASTRAZENECA PHARMACEUTICALS

FINISHED PRODUCT: Nexium™
ACTIVE INGREDIENT: Esomeprazole

Trial title: A Multicenter, Randomized, Double-Blind, Double-Dummy, Parallel-Group Efficacy Study Comparing 8 Weeks of Treatment with Esomeprazole Magnesium (40 mg qd) to Lansoprazole (30 mg qd) for the Healing of Erosive Esophagitis in Patients with Moderate or Severe Erosive Esophagitis

Developmental phase: IIIa
First subject recruited: 14 June 2003
Last subject completed: 6 January 2005
Approval date: 16 August 2006

OBJECTIVES

Primary Objective:

To evaluate the improvement from baseline in reported Health Related Quality of Life (HRQL) using the Quality of Life Questionnaire in Reflux and Dyspepsia (QoLRAD) after 4 and 7 months, for the two study arms, those that received the comprehensive counselling intervention and those that received basic counselling.

Secondary Objectives:

1. To evaluate the improvement from baseline in quality of life (QoLRAD) domains after 1 month for the two study arms.
2. To evaluate the proportion of subjects who achieve an improvement, relief and resolution in symptoms in terms of their Global Overall Symptoms ($\triangle$GOS $\geq$ 2, GOS $\leq$ 2, GOS = 1) during the 7 months for the two study arms.
3. To evaluate any improvement in the Reflux Disease Questionnaire (RDQ) during the 7 months for the two study arms.
4. To evaluate the improvement in overall subject response for Specific Symptoms Subtypes (SSS) after seven months.
5. To measure the overall subject satisfaction after 7 months by means of a Satisfaction Survey (SS) for the two study arms.
6. To measure the overall physician satisfaction after 7 months by means of a Satisfaction Survey (PSS) for the two study arms.
7. To evaluate in those patients that received the counselling Intervention, the perceived value of each component of the Intervention at 7 months.
8. To evaluate the resource utilisation for each study arm due to the burden of disease related to GERD by capturing both direct and indirect costs through a Health Care Resource Utilisation Questionnaire (HRUQ).
9. To evaluate the safety and tolerability of esomeprazole through examination of adverse and serious adverse events.

METHODS

This study evaluated Health-Related Quality of Life, symptoms, patient and physician satisfaction and health economic differences over a period of 7 months between uninvestigated heartburn-predominant dyspepsia patients who have received a standardised disease management comprehensive counselling and those who have received basic counselling, with all subjects receiving esomeprazole 40mg once daily treatment during their first month. The centres were randomly allocated to either providing the comprehensive counselling intervention or providing the basic counselling intervention.

RESULTS

Efficacy

Primary variable:

Change from baseline in Quality of Life (QoLRAD) domains and the overall scores after 4 and 7 months for the two study arms. If there was less than 40% missing data for a subject in the questionnaire within a domain, the missing items will be imputed using the mean score of the non-missing item scores. If more than 40% item scores were missing, no imputation was performed and the domain score was excluded from the analysis.

Secondary variables:

This secondary objective related to quality of life (QoLRAD) was assessed using the change from baseline in Quality of Life (QoLRAD) domains and the overall scores after 1 month of treatment for the two study arms. The missing value imputation will follow the method as stated above in the primary objective.

The symptom relief variable was derived as absolute GOS $\leq$ 2 (Minimal or No problem). The symptom improvement variable was derived as improvement in GOS from baseline (ΔDGOS $\geq$ 2).

The symptom resolution variable was derived as GOS = 1 (No problem). Symptom relief, resolution and improvement for the two study arms were evaluated after 1, 4 and 7 months.

For each of the specific symptom subtypes (SSS), for the subgroup of subjects that are symptomatic at baseline (score $\geq$ 4), the number and proportion of subjects with relief (score $\leq$ 2) of the specific symptoms after 7 months was used as an outcome variable. In addition, the number and proportion of this subgroup of subjects (SSS score $\geq$ 4) with overall symptom relief (GOS $\leq$ 2) at 7 months was used as an outcome variable.

The objective on the Reflux Disease Questionnaire (RDQ) used the symptom severity scores and the change from baseline for all domains and the overall scores after 1, 4 and 7 months.

The number and the percentages of subjects in each satisfaction category for the two study arms were the outcome variables for the objective on patient satisfaction (SS).

The number and the percentages of subjects in each satisfaction category were used as efficacy endpoint for the physician satisfaction survey (PSS).

For the subjects who have received the counselling Intervention, the number and percentage of subjects in each response category for the three components were used as outcome variables for the objective on the comprehensive counselling intervention evaluation (CIEVAL).

The number of resource utilisation events such as hospitalisation, professional visits or laboratory tests or procedures as well as the total Societal and MOH cost variables were used to evaluate the health resource utilisation for the two study arms.

Safety

The incidence, severity and duration of adverse events were used as outcome variables for safety.

The number and proportion of subjects with normal and abnormal physical findings at baseline and at the end of the treatment period as well as the number of subjects whose normal findings at baseline changed to abnormal were considered as safety outcome variables.

REFERENCE

1. Malagelada JR. The continuing dilemma of dyspepsia. Aliment Phamacol Ther 2001; 15 Suppl 1:6-9.

2. Luman W, Ng HS. Survey of dyspepsia management in community. Singapore Med J 2001 42(1):26-9.

3. Agréus L et al.Natural history of gastroesophageal reflux disease and functional abdominal disorders : A population-based study.Am J Gastroenterol 2001; 96: 2905-14.

4. Johanson JF. Critical review of the epidemiology of gastroesophageal reflux disease specific comparisons to asthma and breast cancer. Am J Gastroenterol 2001; 96(8 Suppl):S19-21.

5. Eisen G. The epidemiology of gastroesophageal reflux disease: what we know and what we need to know. Am J Gastroenterol 2001; 96(8 Suppl):S16-8.

6. Silverstein MD, Petterson T, Talley NJ. Initial endoscopy or empirical therapy with or without testing for Helicobacter pylori for dyspepsia: a decision analysis. Gastroenterol 1996;110:72-83.

7. Bytzer P, Talley NJ. Dyspepsia. Ann Intern Med 2001;134(9 Pt 2):815-22.

8. Parkman HP. Nonulcer Dyspepsia. Curr Treat Options Gastroenterol 1998; 1(1):15-19.

9. Caro JJ, Salas M, Ward A. Healing and relapse rates in gastroesophageal reflux disease treated with the newer proton-pump inhibitors lansoprazole, rabeprazole and pantoprazole compared with omeprazol, ranititine and placebo: evidence from randomised clinical trials. Clin Ther 2001; 23(7):998-1017.

10.DiPalma JA. Management of severe gastroesophageal reflux disease. J Clin Gastroenterol 2001; 32(1): 19-26.

11.Armstrong et al. 'Start high' – A better acid suppression strategy for heartburn-dominant uninvestigated dyspepsia (UD) in primary care practice – the CADET-HR study. Can J Gastroenterol 2002; 16, suppl A: 97A.

12.Armstrong et al. Symptom relapse after acute therapy for heartburn-dominant uninvestigated dyspepsia (UD) in primary care practice (PCP) – the CADET-HR study. Can J Gastroenterol 2002; 16, suppl A: 98A.

13.Thomson ABR, Armstrong D, Barkun ANG, et al. The high prevalence of endoscopic abnormalities in 1040 patients with uninvestigated (UD) dyspepsia is not predicted by patients' symptoms (CADET-PE study). Abstract submission to the United European Gastroenterology Week (UEGW) Meeting October 2001, Amsterdam.

14.Blum AL, Arnold R, et al. Short course acid suppressive treatment for patients with functional dyspepsia: results depend on Helicobacter pylori status.Gut 2000; 47:473-480.

15.Huag TT, Wilhelmsen I, Ursin H et al. What are the real problems for patients with functional dyspepsia?Scand J Gastroenterol 1995; 97-100.

16.Talley NJ, Zinsmeister AR, Schleck CD et al. Dyspepsia and dyspepsia subgroups: A population-based study. Gastroenterology 1992; 102: 1259-68.

17.Lydeard S, Jones R. Factors affecting the decision to consult with dyspepsia: comparison of consulters and non-consulters. JR Coll Gen Pract 1989; 39: 495-8.

18.Jackson JL, Kroenk K. The effect of unmet expectations among adults presenting with physical symptoms. Ann Intern Med 2001; 134: 889-897.

19.Owens DM, Nelson DK, Talley NJ. The irritable bowel syndrome: long term prognosis and the physician-patient interaction. Ann Intern Med 1995; 122: 107-112.

20.Tougas G et al.Prevalence and impact of upper gastrointestinal symptoms in the Canadian population : Findings from the Digest study.Am J Gastroenterol 1999; 94: 2845-54.

21.Koloski NA et al.Predictors of health care seeking for irritable bowel syndrome and non-ulcer dyspepsia: a critical review of the literature on symptom and psychosocial factors.Am J Gastroenterol 2001; 96: 1340-9.

22.Armstrong DA, Barkun AN, Chiba N et al. Predictors of treatment response and relapsefor heartburn-dominant uninvestigated dyspepsia (HBDUD) in primary care practice (PCP): the CADET-HR study. Am J Gastroenterol 2002;97: S36.

23. Röhss K. et al. 2001 Esomeprazole 40 mg provides more effective
acid control than standard doses of all other proton pump inhibitors. Gastroenterology 2001; 120(5) (suppl.1):A419.

24.Armstrong DA, Van Zanten V, Barkun A et al.Heartburn-dominant, uninvestigated dyspepsia: a comparison of 'PPI-start' and 'H2-RA-start' management strategies in primary care--the CADET-HR Study.Aliment Pharmacol Ther 2005; 21(10): 1189-202.
Van Zanten V, Bradette M, Chiba N et al.Evidence-based recommendations for short- and long-term management of uninvestigated dyspepsia in primary care: an update of the Canadian Dyspepsia Working Group (CanDys) clinical management tool.Can J Gastroenterol 2005; 19(5): 285-303.

As with any comprehensive clinical trial programme, individual studies may include both approved and non-approved treatment regimens, including doses higher than those approved for clinical use. Before prescribing Nexium™ (esomeprazole), Healthcare Professionals should view their specific country information.